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J952-9

TECHNOLOGY TRANSFER AT THE NATIONAL INSTITUTES OF HEALTH

A TECHNICAL MEMORANDUM

MARCH 1982

Technical Memoranda are issued by OTA on specific subjects analyzed in recent OTA reports or on projects presently in process at OTA. They are issued at the request of Members of Congress who are engaged in committee legislative actions which are expected to be resolved before OTA completes its assessment.

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Preface

The quality and efficiency of health care and, ultimately, improved health of the population depend substantially on the timely and appropriate transfer of medical technologies from the research setting into medical practice. This spreading of technologies must be fast enough so that significant potential benefits are not denied to the population and yet sufficiently paced to assure that enough is known about the safety and appropriate conditions of use of the emerging technologies.

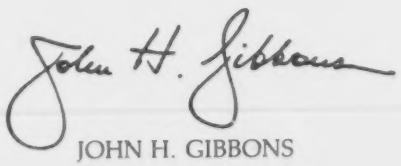
The flow of technologies from research and development (R&D), through evaluation, to their adoption and diffusion in health care settings is thus a crucial aspect of the lifecycle of technology. Congress and many other parties are concerned with how to blend accelerated transfer with informed transfer.

As background to an effort to develop improved policies toward the transfer of medical technologies, the House Committee on Energy and Commerce requested OTA to prepare an examination of current technology transfer and assessment activities of the National Institutes of Health (NIH). This technical memorandum is the result of that examination. It presents general information on biomedical R&D and its relationship to technology transfer, and on the processes of transferring medical technology and of assessing that technology. It discusses the current technology transfer activities of NIH and contains detailed looks at two specific institutes.

The National Cancer Institute has been the focus of substantial congressional concern, particularly over its research directions and its activities in bringing technologies to medical practice. OTA conferred with a large number of academic and other experts regarding these issues.

The National Heart, Lung, and Blood Institute (NHLBI) is also covered in depth. NHLBI has been the single most active institute in terms of an organized approach to technology transfer and the level of such activities.

The main finding of this study is that despite some problems in timely transfer of technologies the most critical problems are: 1) insufficient attention to the development of the basic science base necessary for development of effective technologies; and 2) insufficient attention to the careful, scientific evaluation of the potential benefits, risks, and costs of medical technologies.



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Chapter 1

Introduction

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Chapter 1
Introduction

The ultimate goal of biomedical research is a healthier population. The road to this end result, though, is made up of a great many intermediate goals: for example, improved understanding of basic biological processes; identification of the nature and causes of specific diseases and disabilities; development of ways to identify, prevent, diagnose, or treat diseases; exchange of relevant information; and delivery of services.

One important characteristic that most of the intermediate goals and objectives have in common is their dependence on science and technology. The Office of Technology Assessment (OTA) defines technology as the practical application of organized knowledge. Medical technology is defined as including drugs, devices, and medical and surgical procedures, and the systems in which such technologies are delivered (85). For example, prevention of disease is both a technology in itself and also depends on effective technologies (such as vaccination or public education) for its attainment. Thus, one of the principal outcomes of health-related research is the development and subsequent use of medical technologies.

The process through which technologies are brought to existence and employed in everyday medical practice is not a simple one. It involves, as will be covered later, a series of overlapping and often cyclical stages. For purposes of analysis, OTA divides the process into research and development (R&D), evaluation, diffusion, and use (delivery, financing, etc.).

Technology transfer is often thought of as involving primarily the diffusion stage—the spread of a new technology into common use. However, the success and appropriateness of any technology's transfer or diffusion is heavily dependent on all the stages that precede use. Thus, *technology transfer-related activities* are viewed in this report as involving R&D, evaluation, dissemination of pertinent information, and technology transfer (or diffusion) itself.

The timely and appropriate transfer of technologies from a research setting into medical practice has important implications for the quality of health care, access to care, and the cost of care. For this reason, the transfer of biomedical knowledge into technologies, the assessment of the resulting technologies, and their spread into health care settings continue to be areas of congressional concern.

The National Institutes of Health (NIH) is the primary institution in the United States for the first two of the above processes (the development and the assessment of technologies) and one of the key actors in the third. Because NIH plays such a large and critical role in the substance and the quality of technology transfer, it exerts a powerful influence on the priority given to technology transfer by other groups, on the state of the art of assuring effective transfer, and on the generation and flow of information about technologies, especially their benefits, risks, costs, and readiness for widespread use.

The House Committee on Energy and Commerce requested that OTA examine the role of NIH in assessing and transferring medical technology. This technical memorandum, *Technology Transfer at the National Institutes of Health*, presents the results of that examination.

It was prepared during February and March of 1982. As with all OTA technical memoranda, it contains no policy options for congressional consideration. In response to the committee's primary concerns, it covers NIH in regard to its R&D activities as they relate to the development of medical technologies, its demonstration and control programs and other activities related to transfer of technologies, its efforts to disseminate information on medical technology, and the extent and form of its assessment activities. It draws heavily on earlier OTA studies, especially *Assessing the Efficacy and Safety of Medical Technologies* (85), *The Implications of Cost-Effectiveness Analysis of Medical Technology* (89), *Development of Medical Technology Assessment: Opportunities for Assessment* (88), *Strategies for Medical Technology Assessment* (92), and *Technologies for Determining Cancer Risks From the Environment* (86).

ORGANIZATION OF THE REPORT

Chapters 2 through 5 cover NIH in general. Chapter 2 discusses biomedical R&D, providing background information on the process of biomedical science and its relation to technology development and transfer, on the Nation's and NIH's investment in biomedical research, and on the organization of NIH.

The third chapter presents a description of the process of technology transfer. It is designed to provide a context for the later examinations of current technology transfer activities at NIH. Chapter 4 highlights the role of evaluation of medical technologies as part of the R&D and transfer processes.

Chapter 5 presents and examines the current technology transfer activities engaged in or supported by NIH.

Because of their size, importance, and levels of relevant activities, the National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI) have been highlighted. A major share of attention has been devoted to NCI because of continuing congressional concern over the conflicting pressures on NCI related to transfer and assessment of technologies for preventing, diagnosing, and treating cancers. Chapter 6, therefore, is on NCI. NHLBI has been focused on because it is probably the single most active institute in technology transfer. It has devoted considerable thought and funds to such activities. Thus, chapter 7 covers NHLBI and its transfer and assessment activities.

Chapter 8 presents the findings and conclusions of the study.

Appendix A is a glossary of acronyms. The second appendix contains background material on NIH's process of awarding grants and contracts, including a discussion of peer review. Appendix C is on NHLBI clinical trials.

Chapter 2

Biomedical Research and Development

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Chapter 2

Biomedical Research and Development

INTRODUCTION

Even in this era of increasing disagreement over the allocation of shrinking resources, there is general agreement that a healthy population is the overall goal of efforts in the health sphere. These efforts include a range of activities, from biomedical or health-related research* through the development, application, production, delivery and use of medical technologies. The efforts in these areas are undertaken by the public sector (including Federal, State, and local governments) as well as by the private sector (including nonprofit organizations, universities, industries, and individuals).

Federal participation in the attempts to assure a healthy population have been increasing. Total national health expenditures in 1965 were $42.0 billion; the public share** was $11.0 billion, or 26.1 percent. In 1979, total national health expenditures were $247 billion, with the public share at 42.2 percent (31). Likewise, Federal support for health research and development (R&D) has been increasing, from $1.67 billion in 1970 to $4.93 billion in 1981*** (49). One of the clearest of the Federal responsibilities in health has been to support biomedical research (114).

Health-related research has been defined by the National Institutes of Health (NIH) as follows:

> Health-related research involves systematic study directed toward the development and use of scientific knowledge in the following areas:
> (1) The causes, diagnosis, treatment, control, prevention of and rehabilitation relating to the physical and mental diseases and other crippling impairments of mankind;
> (2) The origin, nature and solution of health problems not identifiable in terms of disease entities;
> (3) Broad fields of science important to or underlying disease and health problems; and
> (4) Research in nutritional problems impairing, contributing to, or otherwise affecting optimum health. (114).

The concepts were recently summarized eloquently by Handler who wrote:

> It is no longer known who first used the term "biomedical science"—perhaps an early clinical investigator desiring to cloak his relatively crude arts with the mantle of precise science, or maybe a fundamental biologist seeking to attract funds more readily available for distinctly medical research. Be that as it may, this is a testimonial to the vitality and enormous utility of "biomedical science"—a spectrum of research extending from the most esoteric explorations of the diverse manifestations of life to astute observations made at the bedside. (30).

The Federal Government supports a range of health-related R&D activities. The basic objective of all of these activities is the production of knowledge (89,114). This knowledge may be in the form of information on health itself, on diseases and disabling conditions, or on environmental influences which impinge on health. Knowledge, in turn, results in new tools and technologies to intervene in the disease process, or to counteract the effects of disease. Some research evaluates the products of previous research while other research investigates the use of technology and other aspects of the health care delivery systems. Perhaps most important, though, is the fact that much of the existing research serves multiple purposes, and some yields results that are more valuable to solve problems in fields other than the field in which the research originated (89).

Health-related R&D have given the health care system and this country much beneficial in-

*In this paper, biomedical and health-related research are used synonymously.

**Of the public share, the Federal share has always been the largest. For example, in 1980, of total public expenditures for personal health care of $77.3 billion, $55.3 billion (71.5 percent) was Federal and $22.1 billion (28.5 percent) was State and local (31).

***Estimated.

formation and many effective technologies, but they are activities necessarily full of uncertainties. These activities may also be expensive—close to $5 billion was spent on health-related R&D in 1981 by the Federal Government alone (49). At the outset, the expenditure of Federal funds for R&D is clearly an investment in the future. Much of this investment represents a potential benefit to all of society and not just to specific individuals or groups. Thus, although a rationale and a precedent for Federal involvement in biomedical R&D exist, it is important that those moneys be spent as wisely as possible and in accord with a balance between public and scientific priorities (89,114).

THE FORM AND RESULTS OF R&D

Ultimately, the desired result of health-related R&D is a healthier population. However, there are a number of diverse activities and intermediate results which occur after a new discovery but before a change in health status is seen. The range of activities is often broken down into loosely defined categories:

1. basic research,
2. applied research,
3. targeted development of technologies,
4. evaluation of technologies, and
5. diffusion and use of technologies.

In general, the first three categories of activities are forms of R&D which result in medical technologies. Medical technologies, then, may be termed the intermediate result of R&D. The last two categories are the utilization of the intermediate results in the refinement and application of those technologies.*

The demarcations between the categories are not clearly defined. Nevertheless, the classifications play an important role in the process of setting health care research priorities, allocating and distributing funds, and evaluating the outcomes or products of R&D efforts. The intended purpose of any given research effort is important at several levels in the health care decisionmaking and policy process. There is constant tension in the decisionmaking process between those who advocate increased funds for basic research, those who feel more work is needed in applying more fully the knowledge and technologies that exist, and those who believe that it is most important to examine what is already in place to determine how it is working and how to make it work better. An important result of these different perceived research needs is that the "label" that is affixed to a given health care program or initiative can be quite important to its ultimate success (89).

The discussion that follows describes the forms of biomedical R&D—basic research, applied research, and development of medical technologies—and defines the immediate result of these activities—medical technology. A brief description of the lifecycle of medical technologies is then included for perspective, but the activities concerned with the evaluation, diffusion and use of the technologies will not be discussed until future chapters.

Basic Research

There are numerous definitions of basic (biomedical) research found in the literature (82,97,98,114). The National Science Foundation (NSF) states that, "In basic research the objective . . . is to gain fuller knowledge or understanding of the fundamental aspects of phenomena and of observable facts without specific applications toward processes or products in mind" (82). The President's Biomedical Research Panel (98) did not formulate a precise definition, but instead suggested characteristics of basic research—that it is an exploring activity, that it requires an atmosphere of uncertainty, and that it must rely heavily on the initiative of the individual investigator or group of investigators. Viewed still another way, basic research pro-

*Another form of research is research on the process involved in performing all of these activities. When this research is done on the use of medical technologies, it is often referred to as health services research.

duces the fundamental science base on which to build improved technologies to prevent and treat disease (97).

There is agreement among biomedical researchers that basic research is essential to the ultimate goal of a healthier population. Comroe and Dripps cited the following examples of the value of basic research:

> When Roentgen discovered X-rays, it was not to enable a cardiologist to visualize the coronary arteries of a patient suffering from angina pectoris; he was studying a basic problem in physics to determine the electrical nature of matter.
>
> When Carl Landsteiner discovered blood groups, it was not part of a program to make blood transfusions safe; he was investigating basic problems in immunology.
>
> When Cournand and Richards passed a catheter into the heart of man, it was not to develop a new method of diagnosing heart disease; they were attempting to measure the oxygen content of mixed venous blood in the right atrium of the heart.
>
> When Shackell developed a technique of freeze drying in 1909, it was not to preserve plasma or its fractions; he was studying a basic problem of the water content of liver and muscles.
>
> When Clarke, collector and amateur breeder of butterflies, studied variations in the color of butterfly wings, he had no idea that it would lead to the discovery of the Rh factor in human blood.
>
> When Davies and Brink devised an electrode for measuring the partial pressure of oxygen, it was not to monitor blood-oxygen in the intensive care unit; they were carrying out basic research (16).

The principle illustrated in these examples were summarized by Handler:

> What stands out in such histories is that each new major technique or procedure enables a leap to unanticipated new understandings and insights, that each new broad biological understanding illuminates a host of pathological circumstances never even considered by the original investigators (30).

Numerous other examples of unanticipated clinical applications from basic research could be cited. In addition, there have been studies of the cost-benefit of basic research (114). For example, Fudenberg (24) estimated that in the 6-year period from 1955 to 1961, monetary savings resulting from the prevention of poliomyelitis cases were $6 million. Savings in 1975 were estimated at $2 million per year, the approximate amount of the total NIH appropriation that year.

If called upon to prove the value of its work, the basic research community can always provide examples. However, these examples can only be compiled retrospectively. Because of its nature, the future outcome of basic research is unknown and speculative.

Applied Research

As with basic research, there are numerous definitions of applied (biomedical) research. NSF (82) states that, "In applied research the objective . . . is to gain knowledge or understanding necessary for determining the means by which a recognized and specific need may be met." Characteristics of applied research include a high degree of certainty about the outcome of the research, the use of facts in the research which are sufficiently abundant and tested so that the outcome can be predicted, a relatively fixed protocol, and carefully planned sequential work schedules (98).

The value of applied research, because its results are more closely linked to treating or preventing disease, is not an issue. Instead, attention has focused on two questions. First, what is the appropriate amount of resources to be spent on applied research in relation to those spent on basic research? Although this question has been answered by numerous researchers and policymakers, others note that it is difficult to see how fixed percentages of future budgets can be set, since ideally the need to do applied research, at a particular time in a particular area of science, depends on what knowledge is available to be applied (98). Second, how can the lag time between the discoveries of basic research and

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their application in applied research be shortened?* This lag was a striking problem around the beginning of the century, but seems to be less of one currently (114).

Development

The distinction between development and applied research is even fuzzier than the one between basic and applied research. Indeed, there are those who do not make one at all. However, development can be defined as "systematic use of the knowledge or understanding gained from research, including design and development of prototypes and processes. It excludes quality control, routine product testing, and production" (98).

While there are many examples of Federal support for development (i.e., the artificial heart), the area is one in which the private sector, and particularly private industry, provides significant funding. This is especially true when the object of the development process is a physical technology, such as a drug or device, and there is a perceived potential for profit (88).

Medical Technology: Definition and Classification

As noted earlier, one of the primary intermediate results of the entire biomedical R&D process is the creation of medical technology. OTA defines technology broadly—as the practical application of organized bodies of knowledge. Medical technology, then, can be defined as the drugs, devices, and medical and surgical procedures used in medical care, and the organizational and supportive systems within which such care is provided.**

Although medical technologies are of many different types and serve a variety of functions, they can be classified into sets. A useful system for classifying medical technologies distinguishes these technologies according to two dimensions—medical purpose and physical nature. Each of these dimensions—medical purpose and physical nature—can be broken down further:

Medical purpose: 1) A *diagnostic* technology helps in determining what disease processes occur in a patient; 2) A *preventive technology* protects an individual from disease; 3) A *therapeutic* or *rehabilitative* technology relieves an individual from disease and its effects; 4) An *organizational* or *administrative* technology is used in management and administration to ensure that health care is delivered as effectively as possible; and 5) A *supportive* technology is used to provide patients, especially those in hospitals, with needed services (e.g., hospital beds and food services).

Physical nature: 1) A *technique* is a purposive application of skills or knowledge, or both, by a health care provider to a patient; 2) A *drug* is any chemical or biological substance that may be applied to, ingested by, or injected into humans in order to prevent, treat, or diagnose disease or other medical conditions; 3) A *device* is any physical item, excluding drugs, used in medical care, and may range from a machine requiring large capital investment to a small instrument or implement; and 4) A *procedure* is a combination, often quite complex, of provider skills or abilities with drugs, devices, or both. With procedures, the predominant factor may be either the product (drug or device), the technique, or the skills of the individual provider performing the procedure.

Medical Technology: Its Lifecycle

In order to place in perspective the role of biomedical R&D in the ultimate application of medical technologies to improve the health of individuals and to set the stage for the discussion of technology transfer, it is useful to briefly describe the lifecycle of medical technologies.***

The development, diffusion, and use of medical technologies is a process that has been described as including at least seven steps (85):

*This lag does not refer to the lag between basic research and adoption of technology in clinical practice. As will be discussed further, the lag between these events has been found too long for some technologies and too short for others.

**This discussion is drawn from two previous OTA reports—*Assessing the Efficacy and Safety of Medical Technologies* (85) and *Development of Medical Technology: Opportunities for Assessment* (88). For an expanded discussion, see those reports.

***As in the previous section, this discussion is drawn from previous OTA reports, particularly *Assessing the Efficacy and Safety of Medical Technology* and *Development of Medical Technology*.

1. Discovery, through research, of new knowledge, and relation of this knowledge to the existing knowledge.
2. Translation of new knowledge, through applied research, into new technology, and development of a strategy for moving the technology into the health care system.
3. Evaluation of the safety and efficacy of new technology through such means as controlled clinical trials.
4. Development and operation of demonstration and control programs to demonstrate feasibility for widespread use.
5. Diffusion of the new technology, beginning with the trials and demonstrations and continuing through a process of increasing acceptance into medical practice.
6. Education of the professional and lay communities in use of the new technology.
7. Skillful and balanced application of the new developments to the population.

This sequence is attractive, because it offers a logical, linear model for understanding the development process and categorizes activities for discussion purposes. In addition, it highlights the fact that it is usually possible to identify a medical innovation prior to widespread diffusion, and thus intervene in the process—either to assure that technologies not properly evaluated for safety and efficacy (at a minimum) are not widely disseminated for clinical use or to speed the process for proven new technologies. Thus, like other models, it represents a desirable order for its component events.

However, medical technologies, like others, in fact emerge from a process that is far less systematic and certainly less linear than implied by the model. Certain steps in the process, especially those concerned with evaluation and demonstration, have often been skipped entirely. An additional weakness of the model is the absence of an acknowledged place for epidemiologic research. Epidemiologic methods have been used in testing efficacy and safety of medical technologies, and they have led to the discovery of causes of disease. For example, epidemiological research has shown that cigarette smoking is the major cause of lung cancer, and thus, control programs for this disease are now possible even though basic research has not as yet discovered the biological mechanism by which smoking causes cancer.

Obviously, biomedical R&D is an important component of the lifecycle of medical technologies. Other important, and overlapping, components include evaluation and technology transfer. These additional components and their interrelationships will be discussed further in chapters 3 through 5.

Assessments and Expectations of Biomedical R&D

Assessment of the performance of biomedical R&D involves one of two kinds of review—review of the individual steps in the R&D process or review of the final results of the R&D, changes in health status. The first kind is an assessment of how well each specific project met its goals. In the case of basic research—where the goal of the study is the production of new knowledge—the measurement of attaining the goal is often the publication output. For applied R&D, production of the targeted product is the measurement of goal achievement. This kind of assessment is also conducted at the organizational level. For example, NIH has conducted studies that measure the correlation between their support effort and biomedical publication output (89).

The second kind of assessment of health-related R&D is concerned with measuring the changes in mortality and morbidity. In this area, the expectations of health research often seem unrealistic. Great cures or changes in health statistics, particularly mortality, can no longer be expected in the short run (114). From 1900 to 1975, the increase in life expectancy at birth was greater than 20 years (56). There is no doubt that medical advances in antibiotics and vaccines and the resulting control of infectious diseases are strongly related to this dramatic increase. In the current era, however, chronic diseases dominate the causes of morbidity and mortality. These diseases are not likely to lend themselves as easily to molecular solutions, since we do not yet understand their mechanisms. Factors difficult to control such as environment, genetics, and

personal health habits play a role. And since chronic diseases generally become evident late in life, gains in life expectancy from their control are likely to be small compared to the years of life saved in children cured of an acute disease (56).

THE ROLE OF NIH IN BIOMEDICAL RESEARCH

The Federal Role

It is estimated that national support for health-related research in fiscal year 1981 totaled $8.47 billion. Of that amount, 58.3 percent, or $4.93 billion, came from the Federal Government. Industry expended $2.7 billion, or 32.0 percent of the total. The remainder, in decreasing order of percent of the total, was spent by State and local governments, voluntary health agencies, other private nonprofit organizations, and private nonprofit foundations (49).

As indicated in table 1, the Federal share of the national support for health R&D has generally decreased over the past decade. The Federal Government has continued to provide the majority of support since 1960, however. Industry's share of the total health R&D effort has steadily increased—in 1960, industry supported 28.6 percent of the total compared with 32.0 percent in 1981 (101). Most expenditures by industry for health-related R&D represent studies relating to drug development (114).

The national support for health R&D as a percentage of all R&D increased rapidly during the 1960's and has remained fairly constant at around 12.4 percent since 1976 (see table 2). A

Table 1.—Federal Health R&D as a Proportion of Total U.S.-Funded Health R&D, 1960-80[a] (dollars in millions)

Year	Health R&D			Federal health R&D as a percent of total health R&D
	Total[b]	Federal	Non-Federal	
1960	$ 884	$ 448	$ 436	50.7%
1961	1,085	574	511	52.9
1962	1,330	782	548	58.8
1963	1,523	919	604	60.3
1964	1,695	1,049	646	61.9
1965	1,890	1,174	716	62.1
1966	2,111	1,316	795	62.3
1967	2,345	1,459	886	62.2
1968	2,568	1,582	986	61.6
1969	2,785	1,674	1,111	60.9
1970	2,846	1,667	1,179	58.6
1971	3,167	1,877	1,290	59.3
1972	3,527	2,147	1,380	60.9
1973	3,735	2,225	1,510	59.6
1974	4,431	2,754	1,677	62.2
1975	4,688	2,832	1,856	60.4
1976[c]	5,084	3,059	2,205	60.2
1977	5,594	3,396	2,198	60.7
1978[c]	6,249	3,811	2,438	61.0
1979	7,097	4,325	2,772	60.9
1980 (est.)[c]	7,894	4,726	3,168	59.9
1981 (est.)	8,456	4,932	3,524	58.3

[a]Excludes research training and construction. Includes U.S.-funded health R&D support spent abroad.
[b]Revised.
[c]Beginning with fiscal year 1975, Federal health R&D data are collected biennially. For agencies other than PHS, HCFA, VA, and the Consumer Product Safety Commission, health R&D figures are estimated by NIH for intervening years.

SOURCES: 1960-80 Data, National Institutes of Health, *1981 NIH Almanac*, NIH publication no. 81-5, 1981.
1981 Data, National Institutes of Health, *Basic Data Relating to the National Institutes of Health: 1981*, May 1981.

Table 2.—U.S. Health R&D as a Proportion of Total U.S. R&D, 1960-80[a]
(dollars in millions)

Year	Total U.S. R&D	U.S. health R&D	Health R&D as a percent of total R&D
1960	$13,523	$ 863	6.4%
1961	14,316	1,058	7.4
1962	15,394	1,289	8.4
1963	17,059	1,475	8.6
1964	18,854	1,645	8.7
1965	20,044	1,833	9.1
1966	21,846	2,050	9.4
1967	23,146	2,276	9.8
1968	24,604	2,488	10.1
1969	25,631[b]	2,697	10.5
1970	25,910[b]	2,765	10.7
1971	26,604[b]	3,063	11.5
1972	28,426[b]	3,418	12.0
1973	30,631[b]	3,587	11.7
1974	32,768[b]	4,236	12.9
1975	35,256[b]	4,478	12.7
1976[c]	38,960[b]	4,848	12.4
1977	43,013[b]	5,318	12.3
1978[c]	48,286[b]	5,942	12.3
1979	54,296[b]	6,732	12.4
1980 (est.)	60,375	7,468	12.4

[a]Excludes research training and construction. Also excludes U.S.-funded R&D support spent abroad.
[b]Revised.
[c]Beginning with fiscal year 1975, Federal health R&D data are collected biennially. For agencies other than PHS, HCFA, VA, and the Consumer Product Safety Commission, health R&D figures are estimated by NIH for intervening years.

SOURCE: National Institutes of Health, *1981 NIH Almanac*, NIH publication no. 81-5, 1981.

similar trend for Federal health R&D expenditures as a proportion of total Federal R&D expenditures can be seen in table 3.* In contrast, the percentage of the Federal health dollar spent on R&D activities has decreased. In 1974, approximately 10 percent of the Federal health dollar supported R&D (114), but in 1980, only 7.9 percent did.**

Agencies Participating in Health R&D

Federal funds for health-related R&D are channeled primarily through NIH. In 1980, NIH support for health R&D accounted for 67.3 percent of the Federal support (48). However, a number of other Federal agencies participate in health R&D. Their contributions are shown in table 4.

*The drop in 1981 may appear because the figures come from budget authority rather than actual expenditures.

**The 7.9 percent figure is derived as follows: 1980 Federal personal health expenditures were $55.3 billion (31). Federal health R&D expenditures were $4,426 million (49). The R&D expenditures as a percent of the sum of the two figures (representing total Federal health expenditures) is 7.9 percent.

Growth of the NIH Program

Prior to World War II, biomedical research in the United States was a small activity, primarily academically based. During the 20-year period following World War II, the field of biomedical research experienced very rapid growth (114). This growth can be seen in table 5. The National Cancer Institute (NCI), authorized in 1973, awarded its first research grants in 1938. At that time, NIH was a separate organization conducting intramural research. The Public Health Service Act of 1944 consolidated and revised existing legislation, making NCI a division in NIH and authorizing NIH to expand its research programs through an extramural grants program. In December 1945, 44 wartime research contracts were transferred to the Public Health Service (PHS) jurisdiction, giving sufficient funds for a general extramural research program. A research grants office was created at NIH in early 1946 to administer these projects and to operate a program of research grants and fellowship awards. This office became the Division of Research Grants (DRG) later that year, and the number and amount of grants began to climb.

Table 3.—Federal Health R&D as a Proportion of Total Federal R&D, Fiscal Years 1960-80[a, b] (dollars in millions)

Year	Total Federal R&D	Federal health R&D	Federal health R&D as a percent of total Federal R&D
1960	$ 7,552	$ 448	5.9%
1961	9,059	574	6.3
1962	10,290	782	7.6
1963	12,495	919	7.4
1964	14,225	1,049	7.4
1965	14,614	1,174	8.0
1966	15,520	1,316	8.6
1967	16,529	1,459	8.8
1968	15,921	1,582	9.9
1969	15,641	1,674	10.7
1970	15,339	1,667	10.9
1971	15,543	1,877	12.1
1972	16,496	2,147	13.0
1973	16,800	2,225	13.2
1974	17,411	2,754	15.8
1975	19,039	2,832	14.9
1976[c]	20,780	3,059	14.7
1977	23,984	3,396	14.2
1978[c]	26,388	3,811	14.4
1979	28,978	4,325	14.9
1980 (est.)[c]	31,878	4,726	14.8
1981	35,523	4,932	13.8

[a]Excludes research training and construction. Includes U.S.-funded health R&D support spent abroad.
[b]Revised.
[c]Beginning with fiscal year 1975, Federal health R&D data are collected biennially. For agencies other than PHS, HCFA, VA, and the Consumer Product Safety Commission, health R&D figures are estimated by NIH for intervening years.

SOURCES: 1960-80 Data, National Institutes of Health, *1981 NIH Almanac*, NIH publication No. 81-5, 1981.
1981 Data, National Science Foundation, "Total Federal R&D Funding Estimated To Increase 7 Percent in 1982 After September Revisions," *Science Resources Studies Highlights*, publication No. NSF 81-321, Dec. 15, 1981.
National Institutes of Health, *Basic Data Relating to the National Institutes of Health: 1981*, May 1981.

Table 4.—Federal Obligations for Health R&D by Agency, 1980[a] (millions of dollars)

Department of Health and Human Services (total)	($3,694.7)
National Institutes of Health	3,181.9
Other Public Health Service agencies	458.6
Other DHHS agencies	54.3
Other agencies (total)	(1,028.6)
Department of Agriculture	147.3
Department of Defense	211.0
Department of Education	32.1
Department of Energy	210.9
Environmental Protection Agency	78.1
Agency for International Development	13.4
National Aeronautics and Space Administration	71.8
National Science Foundation	75.7
Veterans Administration	133.4
Other agencies	54.9
Total	$4,723.4

[a]Estimated.

SOURCE: National Institutes of Health, *Basic Data Relating to the National Institutes of Health: 1981*, May 1981.

The end to the rapid growth period occurred in the late 1960's, when biomedical research support faced competition with other Federal health programs, especially medicare and medicaid, and with the Vietnam War. Table 5 shows that the dollar amount of research grants dropped in 1967, rose again in 1968 and 1969, and dropped again in 1970 before climbing continuously from 1971 on. However, the rise in dollars during the 1970's did not herald the start of a new growth period. Table 6 shows NIH obligations from 1969 through 1980 in actual and constant dollars. When inflation is taken into account, there has been fluctuation throughout the decade ending in a real drop for 1980.

Table 5.—Number and Amount of Research Grants Awarded by the National Institutes of Health, Fiscal Years 1938-80

Year	Number	Amount (dollars in thousands)	Year	Number	Amount (dollars in thousands)
1938	9	$ 91	1960	11,571	$ 198,757
1939	10	68	1961	13,534	272,941
1940	13	61	1962	14,975	372,098
1941	12	78	1963	15,233	430,899
1942	12	78	1964	15,242	497,924
1943	9	49	1965	15,183	538,763
1944	5	53	1966	15,153	600,974
1945	9	85	1967	13,937	593,312
1946	79	890	1968	13,120	626,019
1947	335	3,458	1969	12,435	627,580
1948	1,042	10,152	1970	11,339	602,177
1949	1,130	11,274	1971	11,063	676,245
1950	1,529	13,670	1972	11,524	805,041
1951	1,695	17,130	1973	11,317	815,195
1952	1,798	18,597	1974	13,400	1,070,563
1953	2,084	20,936	1975	13,430	1,116,301
1954	2,855	29,950	1976[a]	14,260	1,239,657
1955	3,256	35,162	1977	14,429	1,386,460
1956	3,430	40,520	1978	15,431	1,577,504
1957	6,186	80,906	1979	17,744	1,883,224
1958	7,028	99,480	1980	18,511	2,086,302
1959	9,056	141,419			

[a]Excludes transition quarter.

SOURCE: National Institutes of Health, *1981 NIH Almanac*, NIH publication No. 81-5, 1981.

Table 6.—NIH Obligations by NIH Component, Fiscal Years 1969-80[a] (in current and constant dollars (millions), excluding programs that have been transferred out)

Fiscal year	Total[b]	NIA	NIAID	NIADDK	NCI	NICHD	NIDR	NIEHS	NEI	NIGMS	NHLBI	NINCDS	DDR[c]	FIC	NLM	
								Current dollars								
1969	$1,037.7	$—	$ 92.6	$140.3	$182.4	$ 71.2	29.6	17.9	$ 21.5	$160.1	$161.9	$104.6	$ 65.3	$13.1	$21.7	
1970	1,057.8	—	97.1	131.5	181.3	76.0	28.7	17.3	22.8	148.1	160.3	97.2	62.6	2.7	19.8	
1971	1,212.0	—	102.1	137.9	232.9	94.7	35.2	20.1	30.0	159.8	194.8	103.4	66.2	3.4	21.4	
1972	1,505.8	—	109.0	153.3	378.6	116.5	43.3	26.4	36.9	173.3	232.6	116.4	75.0	4.2	23.9	
1973	1,523.1	—	103.0	142.8	431.2	111.2	40.9	26.1	34.4	154.0	255.7	107.4	72.8	3.9	25.0	
1974	1,994.4	—	120.8	177.4	581.0	144.1	50.0	32.1	45.2	188.6	327.3	143.5	130.1	5.0	29.2	
1975	2,108.9	—	119.4	173.6	699.3	142.4	50.0	35.9	43.7	189.5	327.8	142.4	127.1	5.7	28.8	
1976	2,238.4	19.2	125.6	174.9	760.5	135.9	50.7	36.8	50.1	186.9	368.6	140.4	130.3	5.7	27.0	
1977	2,582.0	29.9	140.4	219.4	814.9	145.1	55.4	50.9	63.7	204.8	396.5	154.6	137.4	7.7	34.5	
1978	2,828.0	37.1	161.8	259.9	872.4	165.8	61.7	63.9	85.2	230.4	447.8	177.3	144.8	8.3	36.0	
1979	3,184.6	56.5	191.1	302.7	936.7	197.3	65.0	77.5	104.9	277.3	510.0	212.1	154.1	8.9	40.5	
1980	3,428.8	69.7	214.7	340.1	998.0	208.3	67.6	83.6	109.6	312.3	527.1	241.4	169.1	8.7	43.9	
								Constant dollars								Index
1969	1,087.7	—	92.6	140.3	182.4	71.2	29.6	17.9	21.5	160.1	161.9	104.6	65.3	13.1	21.7	100.0
1970	995.3	—	91.4	123.7	170.6	71.5	27.0	16.3	21.5	139.3	150.8	91.5	58.9	2.5	21.7	106.3
1971	1,077.8	—	90.8	122.6	207.1	84.2	31.3	17.9	26.7	142.1	173.2	92.0	58.9	3.0	19.0	112.5
1972	1,275.7	—	92.3	129.9	320.7	98.7	36.7	22.4	31.3	146.8	197.1	98.6	63.5	3.6	20.2	118.0
1973	1,231.6	—	83.3	115.5	348.7	89.9	33.1	21.1	27.8	124.5	206.8	86.8	58.9	3.2	20.2	123.7
1974	1,516.2	—	91.8	134.9	441.7	109.5	38.0	24.4	34.4	143.4	248.9	109.1	98.9	3.8	22.2	131.5
1975	1,448.4	—	82.0	119.2	480.3	97.8	34.3	24.7	30.0	130.2	225.1	97.8	87.3	3.9	19.8	145.6
1976	1,430.5	12.3	80.3	111.8	486.0	86.8	32.4	23.5	32.0	119.4	235.6	89.7	83.3	3.6	17.3	156.5
1977	1,528.4	17.7	83.1	129.9	482.4	85.9	32.8	30.1	37.7	121.2	234.7	91.5	81.3	4.6	20.4	168.9
1978	1,558.0	20.4	89.1	143.2	480.6	91.3	34.0	35.2	46.9	126.9	246.7	97.7	79.8	4.6	19.8	181.5
1979	1,620.8	28.8	97.3	154.1	476.7	100.4	33.1	39.4	53.4	141.1	259.6	107.9	78.4	4.5	20.6	196.5
1980	1,599.3	32.5	100.1	158.6	465.5	97.2	31.5	39.0	51.1	145.7	245.8	112.6	78.9	4.0	20.5	214.4

[a]OD buildings and facilities, are included in totals only. Excludes Foreign Currency Programs. Constant dollars are based on biomedical R&D price index.
[b]ED for 1969 and DCRT for 1969-1970, when these programs were separately budgeted, are shown in totals only.
[c]Includes GRS programs for 1974-1980, formerly spread among IRDs (but 1973 funds released in 1974 are spread).

SOURCE: National Institutes of Health, *Basic Data Relating to the National Institutes of Health: 1981*, May 1981.

ORGANIZATION OF NIH*

NIH is an agency of PHS in the Department of Health and Human Services (DHHS). Its mandate, stated broadly, is to improve human health by increasing understanding of the processes underlying health and acquiring new knowledge to prevent, detect, diagnose, and treat disease and disability.** This mission is pursued via an array of intramural programs conducted at NIH and through an extensive network of extramural grants and contracts to private and public institutions in the United States and other countries. The bulk of the actual research is done extramurally; in 1980, 16.4 percent of NIH's $3.4 billion in obligations were for direct activities including intramural research, while the remaining 83.6 percent were for extramural grants and contracts (49).

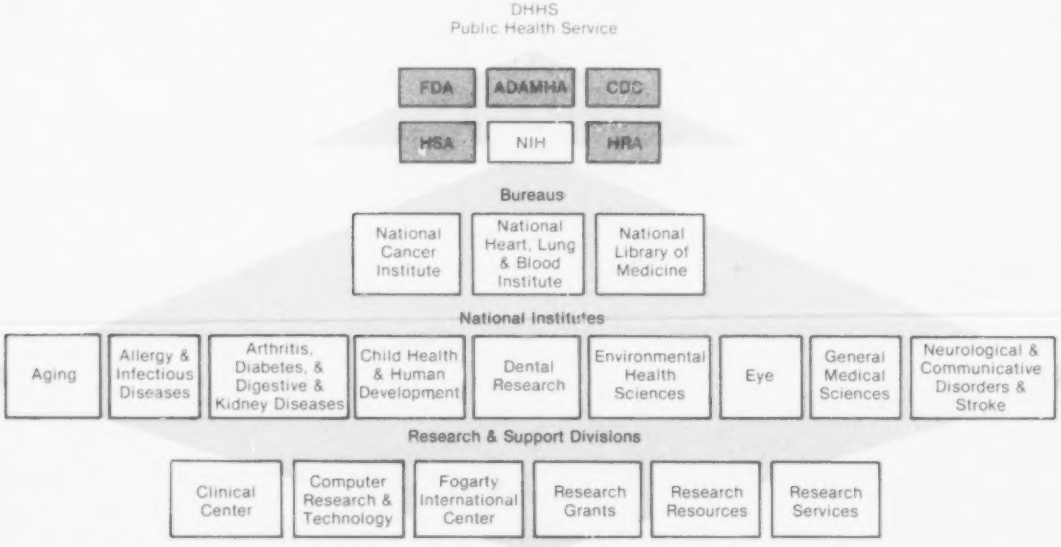
NIH is organized into 11 institutes (two of which have bureau status), the National Library of Medicine (NLM, which is also a bureau), and six research and support divisions. Figure 1 shows the NIH components. The organization has been characterized as loosely categorical, meaning that the various research institutes focus, in a general sense, on particular classes (categories) of diseases or subject matter (7). The scientific content of two of the institutes, the National Institute of Aging and the National Institute of Child Health and Human Development, is organized around biologic processes, and thus tends to cut across the programs of the more traditional institutes. Their organization has been said to solve some, but create other, coordination problems. Overall, the categorical structure has been both praised and criticized (114).

The institutes differ in their statutory bases. Two institutes, NCI and the National Health, Lung, and Blood Institute (NHLBI), have renewable authorizations with monetary ceilings. Other institutes have authorizing statutes with no time or money limitations. One institute, the National Institute of Environmental Health Sciences, has no specific authorizing statute, but depends on section 301 of the Public Health Service Act. The institutes also differ in their re-

*This discussion is drawn primarily from *The Implications of Cost-Effectiveness Analysis of Medical Technology* (89) and *Investigation of the National Institutes of Health* (114).

**The mission will be discussed more fully in ch. 5.

Figure 1.—The Organization of the National Institutes of Health



SOURCE: National Institutes of Health, *Basic Data Relating to the National Institutes of Health: 1981*, May 1981.

lationship to PHS. Two institutes—NCI and NHLBI—as well as NLM, are bureaus in PHS. The remaining institutes and support divisions are division level organizations in PHS. Although the bureaus are an echelon above the divisions, the difference in these designations is largely cosmetic (107) in terms of operations. Additional differences exist among the institutes in the way that they carry out their business, in the philosophy of the staff, and in the mechanisms used to conduct research. Part of these differences are defined in statutes, and part are a result of individual institute determination.

These various semiautonomous organizations are coordinated through the Office of the Director of NIH. The Office of the Director is organized along managerial, rather than substantive, lines and reflects the principle of centralizing supporting services wherever feasible, but placing essentially all program operations within the bureau and division levels. It also reflects the role of the Director, which is primarily to coordinate program and policy development and to integrate resource procurement and execution among the institutes and divisions. There have been longstanding proposals by NIH and others to strengthen the Director's hand, such as additional staff for the Director's Office and limited authority for the transfer of funds from one appropriation to another. They continue to be rejected (107).

Extramural Research Programs

As noted, the extramural research programs comprise the bulk of NIH's budget. And, as shown in table 7, research grants are the primary funding mechanism, budgeted at nearly $2.4 billion out of a total of over $3.6 billion for all progams and operations in fiscal year 1982. Out of the research grants, research project grants receive the bulk of the funds. Program project grants and center grants are two additional important categories of research grants. Most of the remaining extramural dollars go to R&D contracts and to individual and institutional training awards. Technology transfer activities are funded by grant and by contract; these two mechanisms will be described in greater depth. A relatively new funding mechanism, the cooperative agreement, is being used more frequently (as mandated by the Federal Grant and Cooperative Agreement Act of 1977). Some existing grants and contracts are being converted to this mechanism. However, since there are few cooperative agreements in place, they will not be discussed further in this chapter.*

Intramural Research

The conduct of biomedical research within the walls of NIH is the oldest of NIH's missions. Ten of the eleven institutes have intramural programs, with the National Institute of General Medical Sciences as the only exception. The role of the intramural programs in relation to the extramural programs tends to vary from institute to institute. Some activities are similar, except for their precise subject matter, to extramural activities. Others are complementary to the outside world in the sense that they are too expensive, too risky, too uncertain, or have too long a time frame. In addition, there are intramural research activities underway in areas where there is a definite national lack of research resources.

*NCI expects to fund all of its clinical trials by the cooperative agreement mechanism by 1983 (66). An NCI publication notes, "When the purpose of the relationship is the same as that of grants, but the Federal Government anticipates substantial involvement with the recipient during the course of the activity, a cooperative agreement is the funding instrument to be used." (66) The cooperative agreements will be funded using a process similar to the process now used for grants, rather than the one used for contracts.

Table 7.—1982 Continuing Budget Resolution for NIH by Funding Mechanism (in thousands)

	NCI	NHLBI	NIDR	NIADDK	NINCDS	NIAID	NIGMS	NICHD	NEI	NIEHS	NIA	RR	FIC	Total
Research grants														
Research projects:														
Noncompeting projects	$259,834	$211,293	$23,232	$176,217	$107,309	$110,080	$182,311	$89,474	$64,206	$24,788	$29,668	—	—	$1,278,412
Administrative supplementals	6,727	1,455	—	1,920	864	288	878	1,369	650	35	146	—	—	14,332
Competing projects:														
Competing renewals	43,803	46,007	3,078	24,819	29,923	22,375	55,454	19,364	15,594	5,260	6,497	—	—	272,174
New	41,370	42,672	6,841	37,378	20,465	19,682	27,256	19,616	12,328	5,904	13,739	—	—	247,251
Supplemental	1,640	2,932	—	960	325	633	1,017	360	215	—	78	—	—	8,160
Subtotal, competing	86,813	91,611	9,919	63,157	50,173	42,690	83,727	39,340	28,137	11,164	20,314	—	—	527,585
Subtotal, research projects	353,374	304,359	33,151	241,294	158,886	153,058	266,916	130,183	92,993	35,987	50,128	—	—	1,820,329
Research centers:														
Specialized/comprehensive centers	72,131	64,808	8,699	23,401	21,852	4,600	12,407	24,589	4,250	10,052	161	—	—	246,950
General clinical research centers	—	—	—	—	—	—	—	—	—	—	—	$64,324	—	64,324
Biotechnology research centers	—	—	—	—	—	—	—	—	—	—	—	17,712	—	17,712
Laboratory animal sciences & primate research	—	—	—	—	—	—	—	—	—	—	—	24,353	—	24,353
Gorgas Memorial Institute	—	—	—	—	—	—	—	—	—	—	—	—	$1,692	1,692
Subtotal, research centers	72,131	64,808	8,699	23,401	21,852	4,600	12,407	24,589	4,250	10,052	161	106,389	1,692	355,031
Other research:														
Research career programs	4,973	14,476	891	11,276	7,621	3,012	902	3,040	1,378	663	2,166	—	—	50,398
Cancer task forces	13,770	—	—	—	—	—	—	—	—	—	—	—	—	13,770
Clinical education programs	5,800	—	—	—	—	—	—	—	—	—	—	—	—	5,800
Cooperative clinical research	35,500	4,838	—	—	—	—	—	—	1,673	—	—	—	—	42,011
Biomedical research support	—	—	—	—	—	—	—	—	—	—	—	49,544	—	49,544
Minority biomedical support	2,014	2,112	101	1,200	100	109	—	479	118	—	100	18,065	—	24,398
Other research related	5,386	2,178	324	1,778	1,639	762	1,117	528	375	81	739	828	—	15,735
Subtotal, other research	67,443	23,604	1,316	14,254	9,360	3,883	2,019	4,047	3,544	744	3,005	68,437	—	201,656
Total, research grants	492,948	392,771	43,166	278,949	190,098	161,541	281,342	158,819	100,787	46,783	53,294	174,826	1,692	2,377,016
Training														
Individual awards	3,551	4,826	1,414	2,692	3,350	1,901	4,211	1,445	940	606	608	21	—	25,565
Institutional awards	19,248	22,948	2,557	15,257	4,728	6,248	41,839	6,957	2,606	5,646	1,508	658	—	130,200
Total, training	22,799	27,774	3,971	17,949	8,078	8,149	46,050	8,402	3,546	6,252	2,116	679	—	155,765
Research and development contracts	189,224	56,050	2,135	9,675	13,133	10,696	1,307	21,339	5,591	10,206	5,605	2,902	—	327,923
Extramural research	168,450	48,442	14,686	47,514	39,404	42,993	664	26,098	12,405	37,392	14,413	—	—	452,461
Direct operations	41,516	28,100	6,552	12,499	13,058	9,403	8,638	9,473	3,512	2,802	4,245	4,434	7,078	151,310
Management fund	(47,251)	(26,293)	(4,145)	(19,129)	(15,630)	(15,636)	(3,554)	(12,629)	(6,322)	(1,718)	(1,653)	(609)	(375)	(154,944)
Program management	11,857	6,500	1,473	1,605	2,130	3,113	1,861	2,178	1,533	2,775	2,230	1,336	435	39,026
Disease control	55,323	—	—	—	—	—	—	—	—	—	—	—	—	55,323
Instruction	4,500	—	—	—	—	—	—	—	—	—	—	—	—	4,500
Total, IRDs	986,617	559,637	71,983	368,191	265,901	235,895	339,862	226,309	127,374	106,270	81,903	184,177	9,205	3,563,324
											National Library of Medicine			44,402
											Office of the Director			22,562
											Buildings and facilities			9,898
											Total, NIH			3,640,186

SOURCE: Division of Financial Management, Office of the Director, National Institutes of Health

Chapter 3

The Process of Technology Transfer

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Chapter 3

The Process of Technology Transfer

INTRODUCTION

Technology transfer, as an explicit concept, has been used in the health field only in the last decade. Its increasing use has paralleled the increasing development of policies related to medical technology. Definitions are numerous, ranging from the narrow and more specific to the broad and general. The common thread among them, however, is that technology transfer represents a process that includes a series of events. It cannot be described as one activity or one point in time, although discrete activities can certainly be the focus of the process.

The first type of definition is exemplified by Brown, et al. (10), who define technology transfer as "instances where the given technology moves from one situation to another, which may require changes in the technology, the context to which it is moved, or both . . . . [It] diverts the movement of the technology toward increasing specificity [which occurs in the innovation process] by either changing the technology to fit a new application or, conversely, by changing the specificity of an application to fit the technology." The second type, the broad definition, is represented by Dans (18), who defines the term "technology transfer" as "shorthand for the diffusion of technology from its discovery to its appropriate application."

The National Institutes of Health (NIH) stated definition (57) falls into the broad category: "Technology transfer involves the transfer of research findings to the health care delivery system." Yet this definition has been made narrow in its operation by a focus on only two activities—the development of technical consensus on new interventions and the demonstration of these new technologies in the health care system.

As with its definition of medical technology,* OTA defines technology transfer broadly. Medical technology transfer is the process of moving medical technologies from their creation to their application in clinical practice.** It is the means by which medical technologies move through their lifecycle, beginning at the stage where new knowledge is translated into new technology through applied research and ending at the stage where it is applied to the population. Figure 2 depicts the technology transfer process. Though represented in a linear fashion for the purpose of discussion, the process is rarely, if ever, linear. Technology transfer is related to the innovation process*** and can be viewed as the subset of that process that is concerned with innovations that are technologies.

Technology transfer occurs either informally or formally. Informal technology transfer refers to transfer that happens without directed efforts toward putting a technology into clinical use. It usually occurs prior to evaluation of the technology, through activities such as personal experience, peer interaction, and publications. Formal technology transfer is a directed series of activities designed to facilitate *appropriate* application of the technology. These activities are the components of the ideal model of the lifecycle of medical technology development and use, including evaluation activities, demonstration and control programs, and directed education of the professional and lay communities in the use of the new technology. All types of evaluation, then, including technology assessment, are an important part of the formal technology transfer process. Information dissemination activities assist both informal and formal technology transfer.

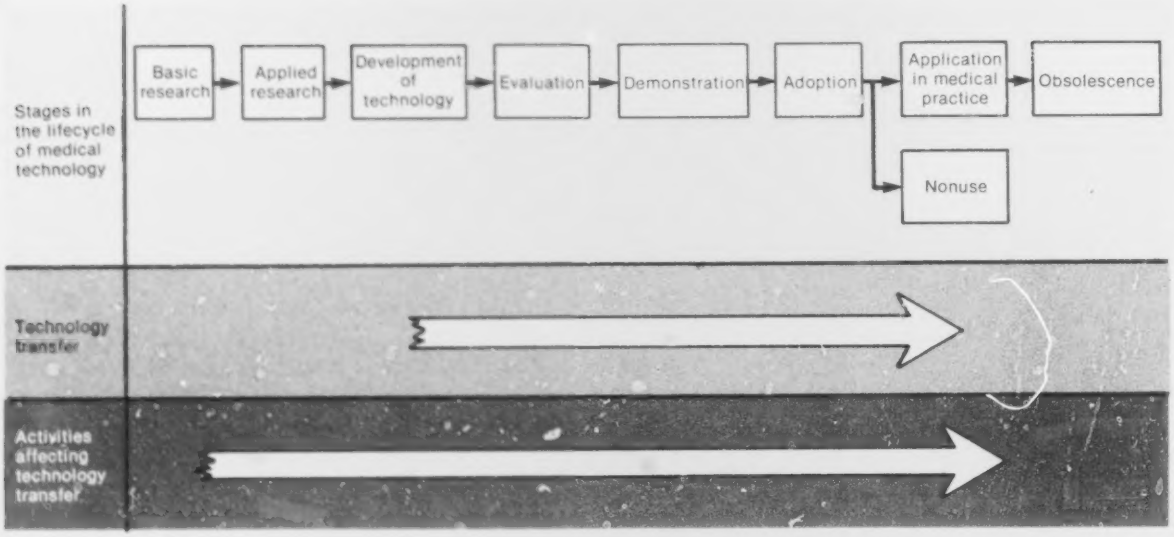
In general, the overall objective of studying technology transfer is to develop (and refine) methods and activities to affect the process

*See ch.2.

**In the context of this report, the term "technology transfer" actually refers to "medical technology transfer." "Medical technology transfer" could also be called "health-related technology transfer;" the important point is that the process occurs in the health care system.

***For a discussion of the innovation process, see *Strategies for Medical Technology Assessment* (92.

Figure 2.—The Process of Technology Transfer



SOURCE: Office of Technology Assessment.

—either to accelerate its pace, to slow it down, to modify it, or to stop it entirely. For technologies showing promise early in their lifecycle or for those evaluated to be useful in certain clinical applications, it is desirable to hasten the process. On the other hand, for technologies not yet evaluated or for those with early indications of being inefficacious or even harmful, it is desirable to slow or, in extreme cases, stop the process.

The specific objective of looking at technology transfer for any particular technology will vary according to that technology's state of development—emerging, new, existing, or new application of existing technology.* In any of these cases, however, there is a need to *identify* the technologies whose movement through the transfer process will be accelerated or slowed. When evaluating the technology transfer process, mechanisms for identification of technologies (at any of the stages of development) should be assessed. These mechanisms at NIH are presented in this report.

The technology process will also vary according to its "clients"—those who learn about the technology and actually put it to use. Clients of the process include: other scientists, who develop the technologies further or discover new applications; industries, who produce, test, and market hard technologies (e.g., drugs and devices); physicians and other health personnel, who apply the technologies; patients, who receive the benefits (and risks); policymakers, who use the information to make decisions affecting future technology transfer; and the general public, who may fall into the other categories at any time.

*Existing technologies are those that have already been "transferred." However, they may, as in the case of radical mastectomy, be candidates for transfer activities that "should have been" conducted prior to their adoption. Once evaluated (or reevaluated), transfer activities can be used to influence adoption under the very specific circumstances.

FACTORS AFFECTING TECHNOLOGY TRANSFER

There is a large body of literature concerned with the diffusion of innovations; by definition, then, it is also concerned with medical technology transfer. It can be divided into three sources:

1. sociological research on the diffusion of innovations in social systems;
2. the effects of communication variables on attitudes and behavior; and
3. the scattered, nontheoretical literature in medicine, consisting of descriptive studies of dissemination and adoption of different medical innovation (92).

Factors affecting technology transfer can be placed into categories, including characteristics of the technology, characteristics of the technology developer, characteristics of individuals using the technology, characteristics of organizations (and their members) using the technology, attitudes, research policies, and regulation and reimbursement policies. As is usually the case with categorization in this area, these categories are created more to facilitate discussion than to convey a sense of discrete sets. In fact, there is a great deal of overlap and interrelationships among them. For example, factors in the last three groups (which are mostly "external" factors) often influence factors in the first four groups ("internal" factors). And although there have been many studies about these factors, the only consensus is that there is much more to learn.

The primary reason for understanding factors which affect technology transfer is to use the knowledge to improve transfer activities. However, understanding these factors and their interrelationships helps to explain why the best efforts by public and private organizations to affect technology transfer do not always work. In the remainder of this section, the factors will be described. The purpose is to place NIH activities, described in chapters 5 through 7, in perspective; thus, the description is not complete.

Characteristics of the Technology

The nature of the technology itself will affect the technology transfer process. Previously mentioned characteristics include the stage of its development (emerging, new, existing, new applications of existing technology) and its medical purpose (preventive, diagnostic, therapeutic, etc.) Other characteristics include its complexity and perceived effectiveness (18), its initial success or failure when tested, and its potential for marketability (where an actual product is the objective) (99).

Characteristics of the Technology Developer

If the new technology developer is an individual, his or her characteristics may influence technology transfer. They include personality, degree of fame, access to other scientists, and ability to appreciate the importance of the discovery (99). For example, an unknown physician named Hammer diagnosed coronary artery occlusion in one of his patients. His published report in 1878 received no attention, and it was 34 years until another scientist named Herrick made the same discovery. Access to resources is another factor important for individual and organizational technology developers. For organizations, particularly companies, their size may influence their ability to develop new technology. It has been found that small companies contribute most to innovation in the early stages of a technological field, but large companies dominate by the time the field matures (92).

Characteristics of Individuals Using the Technology

The effects that characteristics of individual users have on technology transfer have been widely studied, particularly for physicians. Factors influencing transfer include amount of and access to information on the technology; degree to which the individual can be described as cosmopolitan or local; amount of education; preference for the goal of quality health care rather than economic efficiency (10); and the degree of openness to trying new ideas (99).

A crucial distinction has been made between communication that informs physicians about novel technologies and that which influences physicians to act. Clearly, both types are part of the technology transfer process. The most important source of new knowledge about improvements in medical technologies is professional literature. However, physicians cite professional colleagues more often as sources they turn to when actual implementation of new procedures is contemplated. Physicians of greater prestige tend to hear about innovations sooner; they are mentioned by their fellow professionals as influential sources on the medical practice of others (92).

Characteristics of Organizations (and Their Members) Using the Technology

If the technology user is an organization, its organizational structure as well as characteristics of individuals within it will affect technology transfer. There has been a great deal of sociological research in this area, and there are nearly as many theories as there are studies. Not surprisingly, the results have been conflicting. No attempt will be made here to resolve the conflicts, although it should be noted that characteristics of the technology being adopted may affect the effects of the organization.

Greer (29) summarized some of the work on organizational structure variables. Size and resource base are important variables. In general, the larger the organization and the greater its resource base, the more likely it is to adopt innovations. Yet the effects of these variables are often overriden by others—organizational complexity, centralization of decisionmaking, and formalization of rules and behavior.

Attitudes

Attitudes is a class of factors influencing the technology transfer process at all stages. Favorable attitudes can speed up the process, while negative attitudes can slow it down. Attitudes of the individuals potentially adopting or developing a new technology will interact with the attitudes of the society around those individuals in affecting the decision to develop or adopt. For example, if the general attitude of society regarding technological intervention in the birth process had been negative, it is possible that the widespread use of electronic fetal monitoring prior to demonstration of its efficacy would not have occurred. Similarly, that technology has been a relatively recent focus of interest and concern (4), in part because of current increasingly numbers negative attitudes toward such intervention. A final point to be made here is that it is unlikely, if not impossible, that contribution of attitudes to technology transfer will ever be quantified. However, their importance must be recognized.

Research Policies

While it is true that various types of research are actually part of the technology transfer process, it is also true that several types of research policies affect the process. First, the way total research funds are distributed among the stages of the transfer process will affect the transfer which occurs. While basic research is not actually part of technology transfer, it provides the knowledge base for technology development (several examples are provided in ch. 2). Thus, the relative amount of funds devoted to basic research will affect the amount of knowledge ready to be applied, the amount of funds devoted to applied research will affect the *amount* of technologies to be developed and transferred, and so forth. The amount of funds available for evaluation and demonstration will not necessarily affect the amount of technologies transferred, but it will affect the amount of technologies that are

transferred *appropriately* (i.e., those that are transferred after being shown to be efficacious, safe, cost effective, etc.).

Second, the criteria used for setting research priorities, both overall for an organization and within any program for specific projects, will affect the types of technologies transferred. Within an organization, research programs could place priority on filling gaps in knowledge in areas that:

1. Americans fear most (such as cancer);
2. are associated with a greater loss of "quality adjusted life years;"
3. have the greatest cost impact on individuals or society but do not necessarily affect the greatest number of people (such as renal dialysis);
4. have the greatest cost impact as a result of affecting the greatest number of people;
5. have the greatest opportunity for study;
6. happen to be in vogue scientifically or politically; or
7. have the greatest impact as a result of a combination of high cost, high morbidity, and high mortality (18).

Within programs of an organization, projects can be selected according to scientific merit, potential usefulness in clinical applications, political popularity, total cost, and past contributions of the principal investigator, among others.

Finally, the places where research is conducted will affect technology transfer with respect to the degree to which the research organization is plugged into the professional literature or into clinical practice. For example, a top medical school associated with a top teaching hospital is more likely to have a new procedure move into widespread application than a relatively unknown clinic.

Regulation and Reimbursement Policies*

Regulatory actions and more informed reimbursement decisions help to insure that emerging technologies are efficacious, have acceptable risks, and are used appropriately (e.g., are used cost effectively). Private industry determines which drugs and devices it will develop primarily through market-based criteria. To address perceived deficiencies of the market approach, governmental actions infuse additional criteria based on social and political concerns. These governmental actions have generally been regulatory in nature, concentrating on the costs to our health, safety, and environment. Because these costs are diffuse, they can be addressed through collective, governmental actions but not as effectively by individuals. Government's role as a purchaser of technologies, of great significance in health care because of government's role as insurer, has also led to a need to minimize reimbursing for the use of ineffective technologies. This role has also created a need for ways to help decide which among the array of technologies are the most appropriate. In the regulatory process, diffusion into the marketplace is unquestionably slowed, and some technologies are filtered out. Reimbursement policies can also slow (or speed up) diffusion. Slowing the diffusion of new technologies may allow for more informed and timely decisions before widespread use.

The effect on innovation (or technology transfer) from regulatory and reimbursement policies is not simply one of whether the process is inhibited but also whether the alterations in it are unintended or undesirable. Government support of R&D has long sought to alter the process, most notably to accelerate its pace and push it in certain directions. Regulation, particularly when it alters the competitive market, can alter the direction that innovations take. Reimbursement policies probably have more effect on the pace of the process. There is general agreement that competition among medical care providers is typically not based on price. Under current reimbursement policies, there are incentives to adopt all available diagnostic tools and to pursue any therapy anticipated to have any value, especially in hospitals. Third-party coverage currently accounts for about 90 percent of expenditures for hospital care. As the price of technology has little effect on providers and patients under existing health insurance ar-

*This discussion is adapted from *Strategies for Medical Technology Assessment* (92).

rangements, a greater adoption of technology can be expected to occur (and has actually occurred in many cases) than under more price competitive reimbursement arrangements.

At a simple level of comparison, recent changes in current regulatory and third-party reimbursement policies can be thought of as approaching some middle ground from opposite ends of the spectrum. Regulation purposefully slows down the innovation process, particularly at the diffusion stage, and modifications are now being sought (e.g., in premarket approval requirements for drugs) to insure that this slowing of the innovation process is no more than necessary to achieve the regulatory program's objectives. Current reimbursement policies, on the other hand, are seen as boosting the diffusion of new medical technologies beyond what would take place under more price competitive systems, and reforms are being aimed at constraining the adoption process.

Because regulation's purpose is to infuse social criteria into judgments of a new technology's worth, conclusions based on the economic impact of regulatory requirements must be reached with caution. Regulation is expected to change the innovation process. The issues are whether the specific changes were intended and whether the benefits of regulations are worth the price paid in resulting alterations of the innovation process.

In reimbursement policy, a need is to infuse more price sensitivity into the dissemination and use of new medical technologies. Taken together with the regulatory approach, these changes would theoretically: 1) allow into the marketplace innovations which have met social criteria of worthiness, and 2) make it possible for those new technologies which have passed the regulatory test to then compete with each other on a price basis. Curtailing excessive demand by a more price-sensitive approach, however, means changing the conditions of the current medical technology innovation process. Again, the question here is whether such major changes in the demand for new medical technologies will affect the innovation process in unintended and undesirable ways.

METHODS FOR MEASURING AND EVALUATING TECHNOLOGY TRANSFER

Methods for measuring and evaluating medical technology tranfer as a coherent process are not nearly as well developed as methods for measuring the effects of any one part of the process. There are methods available to measure the way physicians adopt a new technology, to evaluate the efficacy of a procedure, or to determine if a demonstration program met its stated goals. Yet there are no well-developed and highly structured research methods that can be used to answer questions about the translation of science to health care (99).

The most promising approaches are refinements of case study methods like those used to trace the scientific lineage of major technological breakthroughs. The most prominent examples of past work are the studies (and their follow-ups) by Comroe and Battelle-Columbus Laboratories for the President's Biomedical Research Panel (99). These past studies, though, do not usually extend beyond the development stage of the process to implementation in medical practice.

An alternative to the case study approach is the assessment of activities which occur as part of the technology transfer process. In this approach, the focus is on the environment in which the technology is transferred rather than on the technology itself. The major weakness of this approach is that it does not look at the entire process at once; however, by examining all activities in one study, the effects of this weakness are lessened. In addition, the connection between the activities and the actual transfer must be assumed, although the influence of other factors is well known. The major strength of the method is the potential for examining any activity in depth, including its relationship to other methods. It is also most useful when the focus of study is one particular organization.

Chapter 4

Evaluation of Medical Technologies

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Chapter 4

Evaluation of Medical Technologies

INTRODUCTION

The process of biomedical research and development (R&D), from basic through applied to development research, produces new medical technologies. As noted in chapter 2, the pace of this process has been accelerating. Frequently, the benefits of new technologies have been clear and convincing. There are numerous examples of new equipment, drugs, and procedures which have significantly advanced the practice of medicine. Some diseases can now be effectively prevented, and medical innovations such as antibiotics have provided effective therapies for a number of other diseases. New diagnostic techniques have often made it possible to detect disease in time to apply an appropriate therapy. Even in cases of diseases for which no effective preventive or therapeutic measures are available, technologies have aided in relief of pain, amelioration of symptoms, and rehabilitation of individuals affected by chronic conditions (88). Finally, some new technology has increased access to health care, some has reduced the cost of care, and some has improved the outcome of care (45).

Yet advances in medical technology development have not occurred without concerns, particularly recently. They may be outlined as follows:

- A number of advances involve significant risks, some intrinsic and some which vary according to the setting in which and the skill with which they are applied. All invasive procedures, including the administration of drugs, surgery and the use of equipment, involve some finite risk to the patient. However, determination of the *safety* of new technologies is crucial, because some level of the risks that may be encountered must be judged acceptable in relation to the potential benefits.
- Many technologies have been widely diffused before their *efficacy** has been established. Concerns about efficacy are raised when a new technology is introduced without proof of its efficacy (e.g., electronic fetal monitoring (3)), when a widely used technology is later shown to be inefficacious (e.g., oral anticoagulants in the treatment of myocardial infarction), or when the relative efficacy of alternative therapies is compared (e.g., the radical mastectomy) (88).
- Health care costs are escalating rapidly. The expanded use of medical technologies is an important factor in the rising costs, imposing *economic* burdens which cause problems for patients, for their families, and for society. Medical technologies contribute to medical care costs in various ways: Some have large capital investments, some require the use of costly supportive services, some present the possibility or requirement of costly followup care, some establish the need for continued use, some are overused after initial proof of reliability of efficacy (particularly diagnostic technologies), and some are used for inappropriate purposes.
- An increasing number of technologies raise *ethical* issues. The concerns may center on the use of the technology (e.g., as amniocentesis or renal dialysis), or on the use of human subjects during research on the technologies (e.g., as many cancer drugs).
- Medical technologies also raise other social issues. For example, with the advent of life-extending technologies such as artificial

*Efficacy refers to the probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under ideal conditions of use. Effectiveness, a term used interchangeably with efficacy by some, refers to the benefit of a technology under average conditions of use (85).

hearts and kidneys, modern technology has challenged society's traditional view of death and dying (88). Critics of the increased use of technologies charge that medicine is being dehumanized by the use of machines and scientific methods (85). Legal issues may arise in several areas, including allocation of resources, liability, and informed consent.

These concerns cover both technical and social issues. Although these sets of issues and the categories within them are often separated for discussion purposes, in fact they are inextricably linked. For example, ethical considerations, seemingly remote from technical matters, can hamper the determination of medical efficacy of some technologies. Although different methods are used to assess the technical and social impacts of new technologies, it must be recognized that problems (and their solutions) cannot truly be separated (88).

Because of these concerns, increasing attention is being focused on the process of medical technology development and use.* In principle, new technology should be introduced into the practice of health care when its benefits to society or individuals outweigh its costs. In practice, however, knowledge of either benefits or costs is often very limited at the time decisions (either formal or informal) regarding the dissemination of a new technology are made (45). Evaluation of technologies is the process in which the knowledge of benefits and costs is gathered and synthesized. It occurs, or should occur, after development and before diffusion and use. Thus, it is a vital component of formal technology transfer.

Like R&D, evaluation covers a broad spectrum of activities. These activities vary according to the nature of the technology being evaluated and according to the criteria being used. The historically most common, and perhaps most important, criteria used in the initial stages of evaluation of health-related technologies are safety, efficacy, technical feasibility, and technical performance. For commercial products (or potentially commercial products, even if developed with public or nonprofit funds), another basic criterion is potential profitability. Other evaluation criteria will then follow, including: effectiveness, reliability, suitability for the goals of its use, cost, cost effectiveness, affordability, potential or actual reimbursement status, repairability, convenience, esthetics, consumer satisfaction, social implications, legal impacts, patent protection, ethical concerns, and so on (93).

Clearly, some evaluation criteria pertain only to "product" technologies, such as devices or drugs. Other evaluation criteria pertain to the medical purpose for which the technology is used. Efficacy and safety, however, are the basic starting points in evaluating the overall utility of a technology. Other criteria, such as legal concerns, are rarely needed if the technology is shown to be inefficacious or unsafe. And, efficacy and safety information is often needed for evaluations of cost effectiveness or potential for reimbursement, for example (85).

The specific objectives of any evaluation depend on the specific criteria being used. In general, the purposes of evaluating medical technologies are:

- To ensure that technologies demonstrated to have potential benefits with acceptable risks are made available rapidly in the private and public sectors. Administrators of public regulatory and financing programs could make sounder and faster decisions regarding the use of the technologies with such information.
- To constrain the diffusion and use of technologies which either lack efficacy or cause excessive harm or whose total societal costs are judged greater than total societal benefits.
- To guide *appropriate* use of all technologies, because technologies are rarely completely inefficacious, unsafe, or undesirable to society.

Thus, the overall goal of evaluation is the production of information that can be used to affect the technology transfer process.

*Ch. 2 describes this process.

METHODS OF EVALUATION*

There are numerous methods available for evaluating medical technologies. The method used varies according to the criteria for evaluation (i.e., efficacy, safety, effectiveness, etc.) and according to the nature of the technology being evaluated (i.e., drug, device, procedure, etc). No technique is universally applicable for every technology. In many instances, less complex methods may be more appropriate than the sophisticated approaches. Frequently, combinations of techniques are used (85). And some methods, particularly those used for evaluating social impacts, are actually combinations of other methods.

This section describes six groups of methods: preclinical, informal, epidemiological and statistical, controlled clinical trials, formal consensus development, and cost-effectiveness analysis/comprehensive technology assessment. Generally, the first five groups** are used in evaluation concerned with technical issues relating to health effects (such as efficacy and safety), while the last two are used in evaluations concerned with social issues. It must be clearly stated that the categories are created to facilitate description; there are overlaps and combinations of methods in the categories used. In particular, the methods used for evaluating social impacts utilize some of the methods in the previous categories. Traditionally, clinical experience, based on informal estimation techniques, has been the most important. Other techniques, such as epidemiological studies, randomized controlled clinical trials, and formal consensus development are being used increasingly.

Preclinical

Many medical technologies are evaluated in biochemical and animal tests prior to human experimentation. There are two purposes for these tests: 1) to gather preliminary evidence to gain the right to test with humans, and 2) to develop performance standard compliance to establish marketability. Biochemical tests include chemical analyses for purity, quantity, and quality of the active agents; analyses for potential pharmacological activity of filler and stabilizing substances; determinations of biocompatibility; and tests for long-term dissolution of body fluids and the possible presence of toxic residues in the production of plastic materials. Animal testing provides a guide to capacity to induce toxcity as well as potential therapeutic activity. Determining the degree of toxicity, or safety, is the major function of animal tests.

A controversial issue is the accuracy of animal models in determing the probable effects of drugs on people. Questions that arise include short-term high dose v. long-term low dose, animal species selection, population size, and controls. These questions are particularly pertinent with respect to carcinogenic agent evaluation. However, despite the inherent problems, an earlier OTA report concluded that animal tests are acceptable models for cancer studies and should probably be regarded as reasonable precursors to clinical studies (87).

Informal

The increasing need to formally evaluate medical technologies, particularly for efficacy and safety, has been described. However, the majority of such evaluations are still based on informal approaches. They may take place during medical school and specialty training and through personal or peer experience. Physicians and other health personnel are constantly exposed to medical technologies throughout medical school, residency, and special courses. Usually, students assume that these technologies are efficacious and safe. Some of them have undergone formal assessments, but most are recommended based on previous experiences or training received by the instructor. Personal experience, the actual use of technologies, is a common qualitative method used to assess both efficacy and safety (and other evaluation criteria). Although it has limited statistical value and

*This section is based largely on OTA's previous report, *Assessing the Efficacy and Safety of Medical Technologies* (85). The section "Cost-Effectiveness Analysis/Comprehensive Technology Assessment" is derived from the 1980 and 1976 OTA reports (89,114).

**Formal consensus development belongs in both categories.

lacks control over scientific quality, it may be advantageous in some cases. Personal knowledge of a patient, for example, may promote beneficial adjustments to the type and level of treatment. Peer experience is more explicit than personal experience; information may be exchanged by items such as journal articles, pamphlets, and personal communication.

Informal techniques are based on the clinical approach of qualitative, artful decisions as compared to the scientific approach of quantitative, mathematical decisions. In any comprehensive system of evaluation, there is a place for both approaches, since each extreme may be appropriate in certain situations. In addition, many assessments require combinations of techniques. Furthermore, cooperation between clinicians and statisticians must exist to attain appropriate decisions when the more rigorous techniques are used.

Epidemiological and Statistical

Epidemiology is the study of the determinants and the distribution of diseases and injuries in human populations. It also incorporates the study of the impact of medical interventions on diseases and injuries. There are a number of epidemiological methods useful in evaluating the effects of medical technologies. Each of these methods involves the collection of data, for at least two groups, on disease manifestations, on changes after the medical intervention (or lack of it), and on certain factors which may be associated with the determinants or distribution of the disease or injury under study. Once the data are collected, statistical analyses are performed to compare the two groups.

The methods differ in the types of data collected, the way the groups for study are selected, and the time frame studied. Retrospective studies compare groups of people who have a disease with those that do not. These studies are designed to determine whether the two populations differ in terms of percentage exposed to certain critical factors. The relationship between oral contraceptives and thromboembolism was established this way. Most information used in retrospective studies is derived directly from the patients, their relatives and friends, and their medical and other records. Thus, there may be doubt about the uniformity, accuracy, and completeness of information (especially on death certificates). In addition to incomplete or biased data, the selection of appropriate comparison groups presents a major problem with this method. There are advantages with the method, however, especially utility, low cost, and quick results.

Prospective studies follow the histories of persons both exposed and unexposed to a critical factor under study. The incidence of deleterious effect (or improvement) resulting from such exposure is then determined for persons in the two groups. A major advantage of prospective studies is the relatively clear designation and selection of both the study and the comparison groups by means of matching charactristics with minimum bias before the disease develops. Disadvantages of these studies include their high cost and long latent periods before results are obtained, the possible occurrence of changes in patients and methods over the duration of the test.

Computer modeling and simulation are methods used most effectively in evaluation when mechanisms of a technology are understood. By simulating physiologic conditions on the computer, the evaluator can apply the technology and obtain information about its effects in different clinical situations without ever involving patients. A major drawback to these methods is that the means of applying them is not yet adequately developed. In addition, they require a fair amount of knowledge about the effects of the technology in order to apply them. They may be particularly useful in evaluating effectiveness of certain technologies, however, and provide information at an accelerated rate at less risk to patients (45).

Controlled Clinical Trials

Controlled clinical trials are a powerful tool in evaluating the impact of technologies on individuals, because they involve the actual controlled application of the technology and objective observation of the results. Perhaps the most

important type of controlled clinical trial is the randomized clinical trial (RCT).* In an RCT, patients who agree to participate are randomly assigned to one of two (or more) groups: one which is exposed to the experimental treatment, and one which is exposed to the standard treatment which may be no therapy such as a placebo (for comparison with a new treatment) or a variation (e.g., a different dosage) of the experimental treatment. Clinical tests and examination of the members of each group are used for evaluations of the relative benefits and risks of the technology.

The principal advantage of RCTs is that they have high internal validity, i.e., they permit relatively unambiguous conclusions as to whether the observed effects of a treatment are due to the technology or some other factor(s). RCTs are the most useful when: 1) the benefit of a new technology is uncertain, or 2) the relative benefits of existing therapies are disputed. There is much statistical theory that supports the scientific utility of the randomization procedures in these trials. And, if a large sample of patients and conditions are tested, external validity (the generalizability of the observed effects to other patient populations, settings, or conditions) may be high.

Yet RCTs have a number of problems. The most controversial problems are ethical; they are based on a concern for both patient and physician rights and responsibilities. Critics of randomization point out that: physicians must make clinical judgments and act according to their consciences (which is precluded by acting according to a protocol); personal physicians must influence whether their patients enter a trial and what treatment is administered; patients must be given the best possible information in consent forms; and patients should be able to choose which treatment is delivered. Other criticisms do not focus on randomization, but instead on the processes used in the trials. Questions about the rights of patients are raised, particularly for children. For example, when can informed consent be given by a child? at what age? with what medical conditions or illnesses? And, who, if not the child, will guard those rights? The long-term effects of treatments or other medical technology interventions can be serious and long in evidencing themselves, particularly in children.

There are those who defend the ethics of using controlled clinical trials. One reason is that physicians can not do just what they "believe" best, since their practice should be based upon sound scientific evidence. Further, if each patient is so unique as to be ineligible for statistical randomization, how can the individual physicians use clinical judgments based on past experience as the optimal guideline for determining the treatment of the next patient? Another defense of RCTs states that the rights of patients are protected in their ability to refuse participation in the trial.

There are also more practical problems involved in the use of RCTs. One is that many trials require a long period of time and large commitments of money, resources, and subjects. In addition, they can be difficult to conduct in settings such as hospital clinics and physicians' office. RCTs can also be especially difficult to conduct for technologies that are already widely diffused. In these situations, administrators and clinicians may be reluctant to make the changes in policies and procedures necessary to conduct the trials. Finally, a priori conclusions on the treatment being evaluated are a major obstacle to conducting RCTs, since such conclusions may subvert the randomization process.

Overall, there are no unequivocal answers to the concerns raised. In general, many articles note the problems, but recommend cautious use of the technique.

Formal Consensus Development

Formal consensus development is an evaluation method which synthesizes evaluation results from earlier, more specific studies. It is generally employed when evidence from previous studies does not lead to an unequivocal decision on the effectiveness, safety, etc. of the technology under consideration. A consensus group is a panel of experts formed both to

*Controlled clinical trials which do not involve randomization are also important, particularly if the treatment may have the potential of curing the disease but killing the patient.

evaluate all pertinent available information, which may range from informal to detailed statistical studies, and to recommend its findings to the medical community.

There are two types of consensus groups relevant here. One type of group evaluates the current state of efficacy and safety knowledge regarding either a particular medical technology or technologies that relate to a specific medical condition. This type of group is found at NIH and will be discussed in depth in chapter 5. A second type of group both analyzes a medical technology, particularly devices, and recommends possible standards to be used in the conduct of future assessments.

Cost-Effectiveness Analysis/ Comprehensive Technology Assessment

This category of methods represents evaluation techniques whose primary feature is that they are actually formal processes. As such, they incorporate other methods of evaluation. Both require basic information on the technical impacts of the technology being assessed and are used when the evaluation criteria are "social" in nature. Another characteristic of these methods is that they are intended to be decision-assisting ones.

Cost-effectiveness analysis (CEA) can be thought of as a synthesis of both the health effects and the economic effects of a technology. In an earlier OTA study, *The Implications of Cost-Effectiveness Analysis of Medical Technology* (89), this method was studied in depth. OTA found that the value of CEA lies more in the process of performing the analysis than in any numerical results which are derived from it. In addition, there is no one "correct" way to do an analysis. The most appropriate approach to CEA and similar methods is to perform it in an open forum such that assumptions and underlying values can be challenged; to identify, measure, and, to the extent possible, value all relevant benefits and costs; and to present the results of the analysis in an "array" of effects rather than forcing them into some aggregate single measure.

Comprehensive technology assessment is a form of policy research that evaluates the short- and long-term social consequences (e.g., societal, economic, political, ethical, legal) of the application or use of technology. Like CEA, comprehensive technology assessment was the focus of an earlier OTA report, *Development of Medical Technology* (88). The principles that apply to CEA also apply here; the major difference is that comprehensive technology assessment covers a broader range of factors, especially those of a social nature.

Chapter 5

Technology Transfer at the National Institutes of Health

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Chapter 5

Technology Transfer at the National Institutes of Health

INTRODUCTION

Obviously, the involvement of the National Institutes of Health (NIH) in technology transfer goes beyond research and development (R&D), as evidenced by its support for activities such as evaluation, demonstration and control programs, information dissemination, and consensus development conferences. What is not obvious, though, is the extent to which NIH should be involved in technology transfer or what its role should be in relation to other public and private organizations. These are questions that need to be addressed by policymakers. Yet they cannot be answered unless the *actual* extent to which NIH contributes to technology transfer, both formally and informally, is known.

The purpose of this chapter is to provide an overview of technology transfer at NIH. OTA finds that a broad spectrum of activities is actually part of the transfer process, although not necessarily formally recognized as such. First, a general overview, including a brief history, of NIH's authority and mission in the area is presented. Next, current activities relating to technology transfer—R&D, clinical trials, consensus development conferences, demonstration and control programs, information dissemination, relationship with industry, and training—are described.

It is beyond the scope of this report to cover all activities at all institutes. Thus, this chapter will present the overview, and the next two chapters will discuss the National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI), the two largest, in depth. At the actual level of operation, the differences among the semiautonomous institutes often exceed the similarities.

ACTIVITIES

General Overview: A Changing Role

The rapid growth of NIH between its beginning as a multiinstitute organization in 1944 and the mid-1960's was in contrast to the limited Federal involvement in other activities in the health field at that time. Faced with its broad mission on one hand and the tradition of limited Federal involvement on the other, NIH made at least three key policy decisions during that period affecting its current and future role in technology transfer (111).

First, the decision was made to foster the development of biomedical research programs in medical schools and their affiliated hospitals. An effect of this decision was to expose medical students to research in the basic medical and clinical sciences and give them sufficient understanding, tools, and motivation to master and use new knowledge as it was developed. Second, the decision to adopt training grants as the main mechanism to foster the training of clinical investigators was made. As a result, clinical departments of medical schools were strengthened, and the link between research and practice was developed. The third major decision was to concentrate on building the research program, while minimizing service-oriented activities, such as disease control programs. At the time, NIH was concerned only indirectly with the diffusion and adoption of new technologies.

Until 1965, NIH was oriented as a supporter of basic bioscience research organized around categories of diseases. This organization satisfied those who were results oriented (7). However, in

1965, Congress authorized the Regional Medical Program to be administered by NIH. This program was designed specifically to facilitate the application of medical advances by using regional medical centers as a focus of technology diffusion and information dissemination (7). According to Tilson, et al. (111), this legislation "epitomizes the emerging congressional interests in making the NIH responsible for the practical application of new knowledge as well as its development."

While not generally considered successful, the Regional Medical Program signaled the start of new trends in congressional interest and action for NIH. The National Cancer Act of 1971 and the National Heart, Blood Vessel, Lung, and Blood Act of 1972 mandated demonstration and control programs in the two institutes. The 1974 cancer amendments mandated a President's Biomedical Research Panel, which, in its study of biomedical and behavioral research at NIH and the Alcohol, Drug Abuse, and Mental Health Administration, covered service-oriented and applied activities. The President's Panel research and report began to focus attention on the overall appropriate role and effectiveness of NIH as a "transfer agent" in the continuum from fundamental research to accepted medical practice (107). Congressional hearings on NIH requested testimony on the subject several years in a row (116,117). And throughout this period, Congress provided special funding for selected elements of knowledge application and dissemination in several of the institutes (97).

Simultaneous with increasing interest in technology transfer activities by Congress was increasing interest by leaders at NIH. In 1975, the mission of NIH was stated as a broad continuing one:

> . . . to advance the health and well being of man through (1) enlarging knowledge and understanding of the normal and pathological processes of the human body, and (2) developing ways in which the providers of medical care can safely and effectively intervene to prevent, treat, or cure diseases and disabilities. NIH pursues this mission through supporting:
>
> - biomedical research and development, including in some instances, demonstration and control;
> - research training;
> - development of research resources; and
> - communication of findings and results of research (56).

The mission essentially implies *knowledge development* without a similar commitment to *knowledge applications*. As a result, there have been several unsuccessful attempts to broaden the statement (114).

In written form, the mission appears to remain the same; there is no corresponding statement in the 1981 Research Plan (58). However, even when the preceding statement was written, and certainly continuing today, there has been considerable attention by NIH to increasing its technology transfer activities. One of the most important results has been the establishment of the Office for Medical Applications of Research in October of 1978. This office will be described further separately.

Another result has been an increasing written focus on transfer activities, including evaluation, consensus development, demonstration and control programs, etc. In 1979 and 1980, the Director of NIH focused attention on technology transfer issues by circulating a document that conceptualizes NIH-sponsored research as a flow of basic science research to its transfer in the field. There are four steps in the process: 1) conducting of basic science research (science base), 2) development of technologies for solving specific problems and testing their application in the field (application), 3) building of a consensus among the scientific community regarding a solution's feasibility followed by its transfer to the field for demonstration (transfer), and 4) training of researchers to ensure the development of basic science research (training) (17). In 1980, the percent of total NIH resources allocated to each respective area was 77, 12, 5, and 5 (57).

An additional example of focus on technology transfer is a compilation of the statutory authority for all of the institutes in the areas of technology assessment and transfer (60). This document demonstrates there is ample authority for transfer activities (as defined in this report) in all institutes. However, the extent of the activities writ-

ten in the laws, and therefore specially funded varies widely from institute to institute. For example, the sections covering the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) mandates such programs as diabetes research and training centers, arthritis demonstration projects, and an information and education center for digestive diseases. The National Eye Institute (NEI) has no similar legislated directive.

R&D and Technology Transfer

R&D activities are not generally considered to be part of technology transfer. However, these activities are very much a part of the technology transfer process—basic research provides the knowledge base, and applied research and development use the knowledge to solve specific problems. In many cases, the solution to the problem is a technology. As noted throughout this report, technologies in the medical area are drugs, devices, medical and surgical procedures used in medical care, and the organizations and support systems within which such care is provided.

Thus, the relative amount of resources devoted to each of the "categories" of R&D—basic research, applied research, and development—affects technology transfer. In addition, the grant awarding process at NIH affects technology transfer. These areas will be discussed below.

Resources for R&D

Table 8 illustrates the amount of resources in 1982 targeted to basic research, applied research, and development activities. In total, R&D activities comprise 94.2 percent of the entire NIH budget. Of the R&D activities, 53.7 percent is for basic research, 35.2 percent is for applied research, and 11.1 percent is for development.

Among the individual institutes and divisions, these figures vary widely. For instance, the National Institute of General Medical Sciences (NIGMS) will spend 86.5 percent of its research dollars on basic research, 12.3 percent on applied research, and only 1.2 percent on development. In contrast, NCI will target 34.2 percent to basic research, 43.3 percent (the bulk) to applied research, and 22.5 percent to development. And, NHLBI's distribution mirrors the total NIH distribution. The variances among the institutes are not surprising, if the missions of the individual institutes are considered. NIGMS exists to support research and research training in the sciences basic to medicine. However, NCI has a number of broader goals in addition to its cancer research, including cancer control programs, and collecting and making available information on cancer (48).

Table 8.—NIH R&D Activities, 1982 (dollars in millions)

	Basic research	Applied research	Development	Subtotal	Training	R&D facilities	Total
NCI	$ 327.9	$ 414.5	$215.4	$ 957.8	$ 23.4	$ 5.4	$ 986.6
NHLBI	302.4	166.3	61.1	529.8	29.8	—	559.6
NIDR	32.1	34.6	0.8	67.5	4.5	—	72.0
NIADDK	219.7	109.0	20.9	349.6	18.6	—	368.2
NINCDS	167.0	77.8	12.5	257.3	8.6	—	265.9
NIAID	143.8	61.5	22.0	227.3	8.6	—	235.9
NIGMS	252.9	36.0	3.5	292.4	47.4	—	339.8
NICHD	111.2	91.5	14.7	217.4	8.9	—	226.3
NEI	64.4	52.3	7.2	123.9	3.5	—	127.4
NIEHS	53.7	42.1	3.9	99.7	6.6	—	106.3
NIA	46.8	29.3	3.4	79.5	2.4	—	81.9
DRR	96.7	76.2	10.6	183.5	0.7	—	184.2
FIC	8.5	0.6	0.1	9.2	—	—	9.2
NLM	3.1	5.7	2.9	11.7	32.7	—	44.4
OD	9.2	9.0	2.6	20.8	1.8	—	22.6
B&F	—	—	—	—	—	9.9	9.9
Total, NIH	$1,839.4	$1,206.4	$381.6	$3,427.4	$197.5	$15.3	$3,640.2

SOURCE: Division of Financial Management, Office of the Director, National Institutes of Health.

In theory, the resources expended on applied R&D are part of technology transfer, albeit at the beginning stages of the process. It could be said, then, that NIH allocates 46 percent of its research dollars to technology transfer, defined broadly. There are several problems with this figure, however. First, the figure does not provide a measure of the transfer *process*, that is, how or whether the basic research results move into applied research and so forth. Second, and perhaps more important, essentially all of NIH's activities, including its more formal transfer activities (e.g., consensus development conferences, demonstration programs) are included in the basic, applied, and development figures. These other activities are actually part of the later stages of the transfer process, and this fact is not reflected. Finally, a related problem is that definitions of basic research, applied research, and development mean different things to different analysts, and the criteria used to classify activities differ from program to program and from year to year (118). An example of this is the comparison between the breakdown in table 8 and the percentages reported for 1980 in the previous section—77 percent of resources for the "Science base," 12 percent for "Applications," 5 percent for "Transfer," and 5 percent for "Training."

Grant Awarding Process

The "dual review system" grant awarding process at NIH, described in appendix B, affects technology transfer in at least three ways. First, the initial review, or peer review, is a mechanism intended to assure that the work being supported is of excellent quality and is likely to produce results. For basic research, the form of the results is uncertain. The important point, though, *is that new knowledge that can be transferred will be created*. For applied research and development, the results are often medical technologies to be transferred. There have been numerous reviews of the peer review system, and its critics have raised questions regarding objectivity and practice in accord with contemporary standards of public agency behavior (114) and the degree to which a different review group would make the same recommendation (12,13). Nevertheless, most reviewers believe strongly that no better system assures such high quality (12,97,114).

Second, the use of advisory councils or boards to approve actual grant awards is intended to assure that the proposals funded are relevant to the priorities of the awarding unit. Thus, when technology transfer activities are a priority for a particular institute, its advisory council can affect whether these activities actually occur. This is particularly true for NCI, NHLBI, and NIADDK, who have a number of mandated formal transfer activities. Third, the members of the initial review groups and advisory councils are generally not government employees, but instead hold full-time positions elsewhere. In the case of the initial review groups, the members are well-known scientists. In the case of the advisory councils, the members are either experts in fields related to the institutes' missions or public members. In each case, the members affect technology transfer by informally reporting on NIH research activities to their "outside" worlds.

Clinical Trials

As one of the most important tools for evaluating the efficacy and safety of medical technologies, clinical trials are a critical component of the technology transfer process. A clinical trial, as described more fully in chapter 4, is a scientific research activity undertaken to prospectively define the effect and value of prophylactic, diagnostic, or therapeutic agents, devices, regimens, and procedures applied to human subjects (114). These trials provide the basis for the testing and orderly application of fundamental research knowledge prior to its general introduction into the health care system. When utilized, they are part of the ideal technology transfer process, because they provide the evidence to prevent the premature diffusion of technologies into medical practice. Similarly, they may be used to accelerate the transfer of new technologies. In an ideal transfer process, clinical trials are done after development research but before demonstration and control projects.

NIH is the single largest supporter of clinical trials in the United States (92). Its involvement in clinical trials in fiscal year 1979 was $136.1

million; this amount represents 4.3 percent of its total obligations that year (49). Since most trials last longer than a year, completion of the trials underway is estimated to cost at least three times the funds spent in 1979.

The early 1970's was the biggest time of growth in clinical trial activity. Between 1971 and 1974, four of the 11 institutes (NCI, NHLBI, the National Insititute of Neurological and Communicative Disorders and Stroke (NINCDS), and NEI) nearly tripled their obligations for major clinical trials (85). In 1975, support for clinical trials at $110 million represented 5 percent of the total budget for that year. Thus, although the increase in total funds between 1975 and 1979 was nearly 24 percent, the rate of increase in clinical trials has decreased. In response to this, NIH noted that such a statement does not take into account the increase in efficiency with which clinical trials are conducted.

Tables 9, 10, and 11 illustrate NIH support for clinical trials during fiscal year 1979. Table 9 delineates clinical trial investment by institute and by type of support. Table 10 shows the number of clinical trials conducted by institute and by

Table 9.—Amount of NIH Support for Clinical Trials Active in Fiscal Year 1979, by Institute for Type of Support

Institute	Extramural support				Intramural support[b]	Total amount of support
	Grant	Contract[a]	Grant and contract	Total		
NIH	$47,304,588[c]	$75,738,768	$1,954,960	$124,998,316	$11,161,800	$136,160,116[c]
NEI	3,141,547	5,378,262	—	8,519,809	85,800	8,605,609
NHLBI	4,006,736	50,933,477	159,788	55,100,001	1,423,500	56,523,501
NIAID	2,435,341	3,827,597	—	6,262,938	234,000	6,496,938
NIAMDD	1,927,658	5,226,975	—	7,154,633	1,085,500	8,240,133
NICHD	3,074,448	556,296	—	3,630,744	552,500	4,183,244
NIDR	221,977	557,672	—	779,649	999,050	1,778,699
NINCDS	1,786,449	439,000	—	2,225,449	435,500	2,660,949
NIGMS	225,750	—	—	225,750	—	225,750
NCI	30,484,682[c]	8,819,489	1,795,172	41,099,343	6,345,950	47,445,293[c]

[a]Contract includes interagency agreements without intramural support.
[b]Intramural support includes intramural support in combination with interagency agreements.
[c]One trial did not report amount of support.

SOURCE: National Institutes of Health, *1979 Inventory of Clinical Trials.*

Table 10.—Number of Clinical Trials Supported by NIH in Fiscal Year 1979, by Institute for Type of Support

Institute	Number of trials supported extramurally				Number of trials conducted-intramurally[b]	Total number of trials
	Grant	Contract[a]	Grant and contract	Total		
NIH	592	212	11	815	171	986
NEI	20	3	—	23	3	26
NHLBI	3	13	1	17	3	20
NIAID	80	34	—	114	6	120
NIAMDD	30	22	—	52	15	67
NICHD	24	6	—	30	2	32
NIDR	2	11	—	13	13	26
NINCDS	17	3	—	20	20	40
NIGMS	1	—	—	1	—	1
NCI	415	120	10	545	109	654

[a]Contract includes interagency agreements without intramural support. Two trials were supported mostly by contract with some intramural support.
[b]Intramural support includes intramural support in combination with interagency agreements. One trial was supported mostly by intramural support with some contract support.

SOURCE: National Institutes of Health, *1979 Inventory of Clinical Trials.*

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Table 11.—Number and Amount of Support for NIH Supported Clinical Trials Active in Fiscal Year 1979, by Institute for Type of Intervention

Institute	Total trials supported in fiscal year 1979[a]		Type of Intervention					
			Therapeutic[a]		Prophylactic[a]		Diagnostic[a]	
	Number[b]	Amount[b]	Number	Amount	Number	Amount	Number	Amount
NIH	666	$112,847,367	494	$50,540,964	118	$58,875,778	53	$3,170,625
NEI	26	8,605,609	22	4,890,194	2	3,415,997	2	299,418
NHLBI	20	56,523,501	10	9,726,605	10	46,796,896	—	—
NIAID	120	6,496,938	57	2,992,347	39	2,697,064	24	807,527
NIAMDD	67	8,240,133	60	7,680,072	4	246,798	3	313,263
NICHD	32	4,183,244	16	2,532,054	15	1,629,175	1	22,015
NIDR	26	1,778,699	7	779,051	17	776,871	2	222,777
NINCDS	40	2,660,949	35	1,565,020	2	959,429	3	136,500
NIGMS	1	225,750	—	—	1	225,750	—	—
NCI	334	24,132,544	287	20,375,621	28	2,127,798	18	1,369,125

[a]Trials in cooperative groups not included.
[b]One trial did not report amount of support. One trial did not specify type of intervention.

SOURCE: National Institutes of Health, *1979 Inventory of Clinical Trials.*

type of support. From these tables, it is clear that the average expenditure per trial ranged widely, from $2.8 million for NHLBI to $54,000 for the National Institute of Allergy and Infectious Diseases (NIAID). The NIH-wide average is $138,000. The tables also indicate that the mechanism of support varies from institute to institute. Most clinical trials are conducted extramurally; the only exception is at the National Institute of Dental Research (NIDR). Of the extramural types of support, the bulk of dollars was spent on contracts. This was true for five of the nine institutes supporting trials. However, the greatest number of trials were conducted by grant; only NHLBI and NEI had a greater number of contracts. It seems reasonable that the largest trials be conducted by a mechanism which allows greater control by the institute.

It is interesting that the two largest sponsors of trials—NHLBI and NCI—use such different mechanisms to fund them. Although the NCI trials are currently being converted to cooperative agreements, there will still be great differences between the mechanisms and processes. Chapters 6 and 7 discuss clinical trials at these institutes in depth.

Table 11 delineates expenditures for trials by three functions of technology: therapeutic, prophylactic, and diagnostic. For the entire NIH, the greatest amount of funds was spent evaluating prophylactic interventions. Therapeutic technologies were close behind, and diagnostic technologies followed at quite a distance. The view of the total NIH picture is somewhat misleading, since most of the trials and most of the dollars were spent on therapeutic technologies if NHLBI figures are excluded.

An earlier OTA report, *Assessing the Efficacy and Safety of Medical Technologies* (85), reported on the expenditures for clinical trials by functions of technology in 1975. At that time, clinical trials investigating therapeutic technologies were predominant. Furthermore, a majority of the trials were conducted to test drugs either in isolation or in combination with another type of technology (with the bulk tested in isolation). More than 300 of the trials tested cancer chemotherapies, while only 25 evaluated surgical procedures. Few trials examined the efficacy of screening or early diagnosis, or primary prevention technologies. Except for the reversal in the relative ranking of trials of prophylactic technologies and of therapeutic ones (caused by the large increase in NHLBI trials of prophylactic technologies), it appears that the findings of the earlier OTA report are still accurate.

NIH's interest in clinical trials does not end with supporting them. Upon their completion, major attention turns toward presentation of the basic results in scientific and professional journals. The primary means of disseminating the analysis of a trial to the research community is publication of the results. Dissemination also occurs through workshops, conferences, and pro-

fessional societies (42). Other examples of interest in clinical trials can be found at the institute level. At NCI, the Board of Scientific Counselors has a Clinical Trials Subcommittee to make recommendations relating to all aspects of the trials (66). If the results of the trials on a particular technology do not lead to a clear decision about its application in clinical practice, NIH has a mechanism to synthesize the evidence for dissemination. This mechanism, the consensus development conference, will be discussed in the next section.

There are several issues that pertain to the role of clinical trials at NIH. One concerns the appropriate amount of investment in clinical trials. This is a difficult issue to address. Clearly, greater and greater amounts of resources are being expended for clinical trials, although the amount as a percent of the total budget has decreased in recent years. On the one hand, investment in clinical trials is extremely important and potentially remunerative since it can prevent new unproved procedures from finding their way into medical practice (and into reimbursement by the Federal programs) (14). However, trials are in many cases quite costly. And, the demand for trials appropriately leads to more trials. Yet resources devoted to trials must necessarily be balanced with more fundamental investigations of etiology and pathophysiology of disease, the foundation of our ability to prevent and treat disease and the source of new clinical hypotheses requiring testing (42).

Another important issue relates to the funding mechanism used to support clinical trials—grant v. contract v. cooperative agreement. Differences between these mechanisms include the amount and type of review on the proposal, the initiation of the idea for the study, the timing of the application process, the amount of control and monitoring which can be conducted by the institutes, and types of end products required (100). In addition, the mechanism may affect the technologies selected to be tested. For grants, the scientific merit of the proposal (rather than its topic) determines award selection. Although there are specific policies that attempt to define the differences between the mechanisms, the distinctions between them are becoming blurred. As noted earlier, the various institutes utilize different mechanisms. Thus, particularly because of the current drive to change grants to cooperative agreements (at least at NCI), the effect of the different mechanisms on trial outcomes should be carefully evaluated.

A related issue is the impact of the budget constraints, in combination with a drive to stabilize the number of competing grant awards, on the ability to begin new clinical trials. While the budget of NIH has not yet suffered the cuts that many other Federal programs have felt and will feel in fiscal years 1981, 1982, and 1983, the rate of budget increase has certainly not kept up with inflation. At the same time, there has been an effort to stabilize the number of competing grant awards to be made each year to eliminate erratic changes in likelihood of meritorious projects being funded. This search for stability, while potentially alleviating one serious problem, has created certain tensions in other areas, notably in the institutes' ability to begin new clinical trials. For instance, in the 1983-85 *Research Plan* published in December 1981 (58), NHLBI states that:

> . . . the most severe impact [of stabilization] will be felt in clinical trials and targeted research, funded under the contract mechanism, where no new efforts can be implemented in 1980-1982 . . . The contract mechanism is best suited to fund clinical trials, and rapid advances in research and developments in cardiovascular and pulmonary treatment techniques necessitate clinical evaluation at a time when no new contracts can be awarded.

Other institutes with smaller budgets and less efforts in the clinical trials areas, such as the National Institute of Child Health and Human Development (NICHD), NIAID, and NIDR, make similar statements.

Office for Medical Applications of Research

Background

In response to the congressional concern with the systematic assessment and transfer of new technologies, the Director of NIH conducted an extensive study of the potential NIH role in this

area. The study resulted in a paper entitled, "The Responsibility of NIH at the Health Research/Care Interface," dated February 28, 1977 (80). This paper defined the problem and the role of the individual institutes and divisions in technology transfer, and expressed the need for a central office to coordinate the existing activities. It took the current status a step further and indicated a need for a formal systematic approach for assessing health care technology and disseminating clinically relevant research findings to the medical practice community and the public.

On May 11, 1977, the Director of NIH initiated a request to the Department of Health, Education, and Welfare (HEW) to establish the Office for Medical Applications of Research (OMAR). This request spelled out the need for new procedures of transferring knowledge that would promote effective community application. The primary mechanism proposed for this task was the development of consensus along with the consideration of the implications involved in the application of the technology. OMAR was informally established in the Office of the Director in September 1977, and was officially created by the Assistant Secretary for Management and Budget of HEW on October 4, 1978 (59).

As published in the Federal Register, OMAR's functions are as follows (59):

1) Advises the Director, NIH, and his senior staff, and provides guidance to the bureaus, institutes, and divisions on medical applications of research;
2) Coordinates, reviews, and facilitates the systematic identification and evaluation of clinically relevant NIH research program information;
3) Promotes the effective transfer of this information to the health care community and through the [National Center for Health Care Technology (NCHCT)] to those agencies requiring such information;
4) Provides a link between technology assessment activities of the bureaus, institutes, and divisions of the NIH and the OHT (Office of Health Technology of DHEW); and
5) Monitors the effectiveness and progress of the assessment and transfer activities of the NIH.

In June of 1980, the Director of NIH appointed a committee to review the activities and mission of OMAR. The review also covered related areas, including technology assessment at NIH, effective coordination of medical applications of research activities at NIH, and the value of a central NIH focus and an apparatus for advice and oversight. A report was issued on September 24, 1980 (59). The committee's findings are generally applicable today, since OMAR has changed little in structure since its inception, although the processes of the office have become more formal. Indeed, the major change affecting the office has occurred outside of NIH: NCHCT was not funded in fiscal year 1982, and thus, OMAR's activities formerly conducted in coordination with NCHCT are either conducted by OMAR alone or not conducted at all. Thus, the sections of the committee's report concerned with the former NCHCT do not apply. At issue today is whether some of the former NCHCT's activities should now be acquired by OMAR. This issue will be discussed further.

Structure and Role

OMAR is a relatively small office, with five professional and four support staff members. During its first 2 years, the program cost approximately $700,000 per year. In 1981, $1.2 million was the approximate figure, exclusive of staff costs and evaluation studies (83).

OMAR's Advisory Committee, consisting of representatives from the various bureaus, institutes, and divisions of NIH, assists OMAR in achieving its goals. Its members and the OMAR staff meet monthly to discuss, determine, and plan consensus development activities and to exchange information relating to other NIH involvement in assessment of biomedical technologies (90). The committee has been in existence since August 1977, even before the formal establishment of OMAR.

The report on OMAR noted that the lack of a clearly defined role for OMAR (except in the development of the consensus conferences) and preoccupation with the administrative details of the meetings have contributed to decreased interest among Advisory Committee members and a high turnover among institute (and division)

representatives. The committee and its subcommittees have been effective, however, in the development of issue papers. Topics covered in the issued papers have included the activities and mandates of NIH, the development of evaluation schema, methods for updating consensus statements, and advice on the definition and reporting of emerging technologies. The committee has also served as a principal means for sharing information about technology transfer issues within NIH (59).

Consensus Development

OMAR's primary activity has been the administration of the consensus development program at NIH and support of the actual consensus conferences. The consensus development conferences bring together scientists, practitioners, consumers, and others in an effort to reach general agreement on the safety and efficacy of medical technologies. The technologies of interest may be emerging or may be in general use. Recent conferences have tended toward examining emerging technologies, while early conferences generally focused on existing—and sometimes controversial—technologies. The technologies studied may be drugs, devices or medical, surgical, or dental procedures. Since the first conference in September 1977, there have been 32 conferences held and four more are currently scheduled. Table 12 lists the topics, dates, and sponsors.

The first step in planning a consensus development conference is the selection of the technology to be assessed. Since this activity occurs at the individual institute or division level, procedures vary widely. Before a conference topic is finally selected and scheduled at OMAR, it will have been discussed and reviewed for 2 to 15 months at the institute level. It will also have been discussed by the OMAR Advisory Committee to generate suggestions and interest from other institutes that may have escaped the original sponsors. Should the case arise (and it has not to date) that there are more topics identified for conferences than OMAR has the resources to support, the OMAR Advisory Committee would be the body to recommend a priority order in which the conferences would be held.

Once the conference topic has been identified, the planning process begins. OMAR provides the initiative and logistic support and offers guidance based on the experiences with previous consensus development exercises. The planning period typically lasts 9 to 18 months (90). A number of planning meetings, first involving only NIH and OMAR staff, and later involving outside experts, are usually held to delineate the key issues. Also determined during the meetings are the specific questions surrounding the technology under discussion and the approaches to be used in reaching consensus. Individual experts may prepare papers prior to the meeting summarizing the state of the science; alternatively, or in addition, task forces are asked to produce draft documents for consideration at the conferences.

Consensus development panels are carefully constituted to reflect the range of individuals and organizations with expertise and interest in the use of the technologies. They include researchers in relevant fields, members of the pertinent clinical specialties, health care consumers, and others. Without question, however, the panel is overwhelmingly scientific, often reflecting the orientation of its sponsor. The conference is open to the public and audience participation is encouraged.

Most NIH consensus development conferences have used some variation of the following general format. The conference begins with a plenary session, during which individual experts or representatives of task forces present information on the state of the science. Comments by panelists may follow. Also, members of the audience may ask questions or provide comments. In some cases, work groups or task forces then meet to discuss specific aspects of the technology. In a closed session, the panel then convenes in an attempt to reach a consensus on the relevant issues. At the final plenary session, the consensus statement is presented to the audience for comment. At times, the audience comments are incorporated. Panel members who disagree with major conclusions may issue a minority report. A minority report has only been issued once.

Consensus statements are not, and do not attempt to be, regulations on the "proper" practice

Table 12.—NIH Consensus Development Meetings, September 1977 Through November 1982, Office for Medical Applications of Research

Sponsors	Title	Dates held
NCI	Breast Cancer Screening	Sept. 14-16, 1977
NCI	Educational Needs of Physicians and the Public Regarding Asbestos Exposure	May 22, 1978
NIDR	Dental Implants Benefit and Risk	June 13-14, 1978
NCI	Mass Screening for Colo-Rectal Cancer	June 26-28, 1978
NIA	Treatable Brain Diseases in the Elderly	July 10-11, 1978
NINCDS	Indications for Tonsillectomy and Adenoidectomy: Phase I	July 20, 1978
NIAID	Availability of Insect Sting Kits to Non-physicians	Sept. 14, 1978
NCI	Mass Screening for Lung Cancer	Sept. 18-20, 1978
NIGMS	Supportive Therapy in Burn Care	Nov. 10-11, 1978
NIAMDD	Surgical Treatment of Morbid Obesity	Dec. 4-5, 1978
Interagency Committee on New Therapies for Pain and Discomfort (Organizer)	Pain, Discomfort, and Humanitarian Care	Feb. 16, 1979
NICHD	Antenatal Diagnosis	Mar. 5-7, 1979
NHLBI	Transfusion Therapy in Pregnant Sickle Cell Disease Patients	Apr. 23-24, 1979
NHLBI	Improving Clinical and Consumer Use of Blood Pressure Measuring Devices	Apr. 26-27, 1979
NCI	The Treatment of Primary Breast Cancer: Management of Local Disease	June 5, 1979
NCI	Steroid Receptors in Breast Cancer	June 27-29, 1979
NEI	Intraocular Lens Implantation	Sept. 10-11, 1979
NIA	Estrogen Use and Postmenopausal Women	Sept. 13-14, 1979
NIAID	Amantadine: Does It Have a Role in the Prevention and Treatment of Influenza?	Oct. 15-16, 1979
DRS	The Use of Microprocessor-Based "Intelligent" Machines in Patient Care	Oct. 17-19, 1979
NIDR	Removal of Third Molars	Nov. 28-30, 1979
NHLBI	Thrombolytic Therapy in Thrombosis	Apr. 10-12, 1980
NINCDS	Febrile Seizures	May 19-21, 1980
NCI	Adjuvant Chemotherapy of Breast Cancer	July 14-16, 1980
NCI, NIA, NICHD, NCHCT	Cervical Cancer Screening: The Pap Smear	July 23-25, 1980
NIAMDD	Endoscopy in Upper GI Bleeding	Aug. 20-22, 1980
NICHD	Childbirth by Cesarean Delivery	Sept. 22-23, 1980
NCI	CEA and Immunodiagnoses	Sept. 29-Oct. 1, 1980
NHLBI, NCHCT	Coronary Bypass Surgery	Dec. 3-5, 1980
NINCDS, NIAID, NIAMDD, NICHD, NIEHS, DRS	Reye's Syndrome Diagnosis and Treatment	Mar. 2-4, 1981
NINCDS, NCI	CT Scanning of the Brain	Nov. 4-6, 1981
NIAID	The Effect of Diet on Hyperactivity	Jan. 13-15, 1982
NIADDK	Hip Joint Replacement	Mar. 1-3, 1982
CC	Critical Care Medicine	Summer 1982
NIAID	Immunotherapy - Treatment of Insect Sting Allergy	Oct. 6-8, 1982
DRS	Validation of Biomaterials	Nov. 1-3, 1982

SOURCE: Office for Medical Applications of Research, National Institutes of Health.

of medicine. Rather they are attempts to represent the best current thinking by a group of scientific experts and others in a position to make judgments on safety and efficacy. Consensus conferences differ from standard state-of-the-art meetings in that consensus panels must consider and seek closure on specific sets of questions, and the format of the conference has been predetermined.

Dissemination

Those conducting consensus development conferences hope that by supplying practitioners with critiques of complex medical technologies, the consensus reports will contribute to an improvement in the quality of medical practice. Dissemination of the consensus statements and supporting materials is thus an essential part of the program. Practicing physicians and others in the health care system, the biomedical research community, and the public are the groups targeted to receive the statements. OMAR assists in the actual dissemination and in the monitoring of the following dissemination activities. Consensus materials and information have been published in the three American medical journals with the largest circulation—the *Journal of the American Medical Association*, the *New England Journal of Medicine*, and the *Annals of Internal Medicine*. Distribution through State medical journals, other scientific publications, mainstream periodicals, and the general press is encouraged, though such distribution is not directly initiated by OMAR (90). A brief review of the literature by OMAR found that most of the consensus reports were published in at least two journals (80). OMAR actually publishes summaries of the conferences in a periodic publication, *NIH Consensus Development Conference Summaries* (81), and distributes it to requestors on its mailing list of over 21,000 names. In addition, the conference reports have been indexed in the National Library of Medicine's *Index Medicus* since the winter of 1980, making their existence even more widely known.

OMAR's information dissemination activities are focused solely on consensus conferences. These activities are not formally coordinated with NIH's other numerous information dissemination activities, although coordination of information offices is accomplished to a degree through periodic meetings with the Associate Director for Communications. According to the report of the Oversight Committee for OMAR (59), the liaison between the Office of Communications and OMAR is satisfactory. However, work on use of nonpublished media and interpersonal networks discussed by a Task Force on Communications (established in 1975 and abolished in 1978) is not receiving adequate effort. In 1981, a subcommittee on communications of the OMAR Advisory Committee prepared an OMAR dissemination plan. This plan is awaiting implementation.

Other Activities

Since its creation, OMAR has provided a conduit for requests from other agencies for technical advice, generally in the areas of reimbursement and specific technologies. OMAR's function has been to receive the requests, channel them to the appropriate institutes for action, and return the completed response to the requesting agency. For reimbursement advice, NIH provides only technical material on the acceptability of a procedure in medical practice; it does not actually develop reimbursement recommendations. These recommendations are currently developed for the Health Care Financing Administration (HCFA) by an office of the Assistant Secretary for Health, DHHS. Formerly, NCHCT developed the recommendations. In 1979 and 1980, NIH answered 63 such requests (59). For specific technologies, OMAR had channeled requests from NCHCT to the various institutes to identify experts to prepare overview papers. This activity does not currently occur, although the mechanism is still in place.

Discussion

In the following ways, OMAR and its activities, particularly the consensus development program, have successfully contributed to appropriate technology transfer. The consensus statements and supporting materials provide a resource to assist members of the health care community and the public in making sound decisions regarding the use of medical and surgical procedures, drugs, and devices. The program has also helped scientists and policymakers to

identify gaps in current knowledge and opportunities for further research (95). And in contrast to some original concern that consensus development would be thought to stifle innovation, there have been reports that the inclusion of recommendations for further research in the statements actually fosters innovation (95).

The program has several weaknesses, however. One limitation of the program is in the process itself. For instance, the use of adversary groups and task forces has been almost entirely abandoned recently, and the questions posed have been strictly on issues on which there is enough factual evidence to reach agreement. For the purpose of synthesizing available knowledge, this approach may be adequate (assuming that the available knowledge is all included and understood). Some critics still believe that for the purposes of identifying gaps in knowledge and needs for future research this approach is weak (92). NIH does not agree with this judgment, however, arguing that in instances where consensus cannot be reached, the panels identify areas of needed research. Even when the clearly controversial issues are tackled, critics have voiced concern that the fact that consensus has been reached means that the statements are only bland generalities that represent the lowest common denominator of the debate, and as such are far from the cutting edge of progress (103).

As the office responsible for monitoring the progress and effectiveness of the consensus development program, OMAR has launched two major evaluative efforts. One study will compare alternative strategies for conducting NIH consensus development activities (a look at the process), and another will assess the impact of the conferences.

Apart from questions over the method and process of consensus development, an issue remaining to be resolved is whether the role of OMAR should be expanded, since NCHCT has been disbanded. Although NCHCT's specific coordination activities are no longer being performed, OMAR is basically functioning the same way today as it did before NCHCT's demise. That is, it utilizes the same intra-NIH procedures for selecting consensus development conference topics, planning the conferences, and disseminating information on them as it did before; and it assists HCFA with technical advice related to reimbursement as it always did. The difference is that reimbursement requests come from a temporary office in the Assistant Secretary for Health's office instead of from NCHCT. The assessments done with OMAR's assistance focus on safety and efficacy rather than ethical, legal, economic, and political issues. However, OMAR does not have the mandate to conduct such broad-based studies. Additionally, there is no NIH-wide mandate to systematically identify emerging and existing technologies in need of review, as there had been in NCHCT's day. Several institutes do perform this activity—NHLBI's program, though, is certainly the most formalized.

Demonstration and Control Programs

Demonstration and control programs, like consensus development conferences, are formal technology transfer activities. They are undertaken specifically to assure that new technologies that have been shown to be safe and efficacious are applied in clinical practice in the most effective ways. In 1975, the Director of NIH defined the terms as follows:

> Demonstration means either showing that something works, such as patient education, or showing that something that works in an ideal setting works in a practical field setting. Control has as its goal the reduction of disease, preferably by prevention, and is the ultimate objective of biomedical research. However, its meaning has changed to refer to the extension or diffusion throughout the health care system of an intervention, technology or some other change in the substance of medical practice (114).

Demonstration and control programs are generally discussed together as a category of activities (56,60,114). Technically, they are overlapping activities. Demonstration projects are not always concerned with the control of disease in the prevention sense, although demonstration of the application of any medical technology is intended to affect some aspect of eventual disease reduction. Control programs, however, usually comprise a broad range of activities, of which

the most important are demonstration projects. In a discussion of control programs at NHLBI, a study panel concluded that "well-conceived demonstration projects will conserve limited resources, save money, and reduce the frustration that inevitably results from premature and ill-conceived projects. They will ensure that new programs are well-tested before they are committed to general use" (56).

Demonstration and control programs are not a new NIH activity, but actually started with the National Cancer Institute Act of 1937. In 1946, the Cancer Control Branch was established within NCI to provide grants to State health agencies for cancer control activities. As new categorical institutes were established at NIH, additional disease control activities were added. Some, such as the Heart Disease Control Program, were identified as discrete and visible programs, while others were not separately categorized and funded as control programs per se. In the early 1960's, the control programs of NIH were transferred to the Public Health Service Bureau of State Services. Then, in 1968, the control programs as they existed were phased out, and some components were transferred to the Regional Medical Programs. Demonstration and control activities returned to NIH with the enactment of the National Cancer Act of 1971 and the Heart, Blood Vessel, Lung, and Blood Act of 1972. These activities were expanded to other disease areas with the passage of the National Diabetes Mellitus Research and Education Act of 1974 and the National Arthritis Act of 1974.

The amount of demonstration and control activity varies widely among the institutes. The largest effort, by far, is the Cancer Control Program at NCI; it is the only control program with a line item in the budget. This line started at $5 million in 1973, reached a high of $70 million in 1979, and is set at $55 million for 1982. Corresponding figures for other institutes are not available, but if they were, most would be less than half the NCI amount. The National Research and Demonstration Centers Program of NHLBI is the second largest demonstration and control program at NIH. Programs at NCI and NHLBI are discussed in depth in chapters 6 and 7.

An examination of the statutory authorities for the institutes reveals that demonstration and control are mentioned for only six of the 11 institutes—NCI, NHLBI, NIADDK, NIGMS, NIDR, and the National Institute on Aging (NIA). Of these, only four (NCI, NIADDK, and NIGMS) have specific programs authorized. While there are currently examples of such programs at eight of the institutes, it is clear that the efforts are greater when Congress has specifically mandated the activities.

Some examples of demonstration and control programs are as follows (58):

1. NIAID—accelerated vaccine development.
2. NIADDK—demonstration of prolonged cadaver graft survival with multiple pretransplantation blood transfusions.
3. NCI—numerous activities coordinated by a new Division of Resources, Centers, and Community Activities.
4. NICHD—new methods for managing the diabetic condition early in pregnancy will be tested for effectiveness in reducing the risk of congenital defects among offspring.
5. NIDR—demonstration of fluoride-containing agents under the National Caries Program.
6. NIGMS—development of artificial skin for burn victims.
7. NHLBI—program of National Research and Demonstration Centers.
8. NINCDS—Comprehensive Stroke Centers.

The general orientation of NIH is that demonstration and control programs should involve the establishment of innovative disease control technology through controlled, time-limited projects conducted in limited populations (114). Thus, most of the institutes have some interest in demonstration and control activities.

Information Dissemination

Information dissemination is essential for technology transfer to occur. It is the means by which results travel from one stage in a technology's lifecycle to another. All information dissemination activities, therefore, affect technology transfer. The activities associated with the more formal technology transfer programs, such

as the consensus development program and demonstration and control programs, are designed to disseminate information about the appropriate clinical use of medical technologies. On the other hand, the dissemination activities associated with programs in the earlier stage in the technology's life (such as R&D or evaluation) are designed to assure that basic knowledge can be translated into solutions potentially applicable to improving health.

Along with its responsibility to develop and evaluate new biomedical knowledge, NIH has had, since its early days, an implicit responsibility to disseminate information about research results to the research community, the health professional community, and the public in an effective and timely manner. However, this responsibility has been made more explicit by Congress over the past decade, reflecting both a feeling that dissemination activities are important and a criticism of NIH's less-than-vigorous efforts in the past (114).

Of the 11 institutes, only four do not have specific mandates to disseminate research results (NIGMS, NEI, NIAID, and NINCDS). The statutory authorities for the seven remaining institutes vary according to the specificity of their dissemination programs. The most specific law concerns NIADDK. It mandates several programs of which information dissemination is a major component, including: the Diabetes Data Group and Clearinghouse, Diabetes Research and Training Centers, arthritis demonstration projects, the Arthritis Data System, multipurpose arthritis centers, and the National Digestive Diseases Education and Information Clearinghouse. NCI and NHLBI also have several designated programs in their statutes, while NIDR, NIA, NICHD, and the National Institute of Environmental Health Sciences (NIEHS) have less specific directives.

Clearly, where Congress has created special provisions for other technology transfer activities, it has also stressed information dissemination. This is evidenced in the original and amended versions of the National Cancer Act of 1971, the National Arthritis Act of 1974, the National Diabetes Mellitus Research and Education Act of 1974. The trend which started with the National Cancer Act has continued and strengthened—the latest amendments to the NIH authority focused on NIADDK, and it is NIADDK that has the most specific dissemination programs.

In 1974, the Director of NIH established a Committee on Dissemination of Research Results to review NIH-wide dissemination activities and develop specific recommendations. This committee produced yearly reports through August 1977, when the fourth and final report was written (53). When OMAR was created, the committee ceased to function. The committee divided the task of information dissemination into programs for three target audiences: research scientists, practicing physicians and other health professionals, and the general public. Although formal yearly progress reports are no longer written, the target groups remain the same.

Dissemination to Scientists

In the area of scientist-to-scientist communication, the primary mechanism is through publication in the more than 2,200 scholarly and scientific journals. This mechanism, which includes critical review of the results as a condition of publication, safeguards the scientific community against widespread diffusion of incorrect information.

It is generally agreed that this mechanism is effective (114). That NIH ranks fairly high in the scientific literature is evidenced by a recent survey of 1,000 scientist-authors whose published works from 1965 to 1978 were considered the most cited in scientific literature (55). There were 84 NIH intramural scientists among the 1,000, or 10.5 percent of the estimated 800 authors who published in fields relevant to the NIH mission.

The National Library of Medicine (NLM) is NIH's largest activity in the area of scientific information acquisition and storage for easy retrieval.* A major role of NLM is to provide mechanisms for dissemination of information, including 20 online data bases directly accessible

*NLM was the topic of study in an OTA staff paper in 1981 (91) and in a technical memorandum to be completed in April 1982.

at more than 1,530 institutions (91), the Regional Medical Library Program and the National Medical Audiovisual Center. Although there are unresolved issues concerning NLM's future growth and directions, it is regarded as an excellent program.

Dissemination to Health Professionals

In the area of communication of research findings to health professionals, it is not sufficient simply to provide volumes of study results no matter how worthy they may be. A busy practitioner would be inundated by the sheer volume of information if he or she received the full output of published results. For this reason, it is essential that there be a sorting-out process and that communication efforts be concentrated on the portion of research output that is ready for use in clinical settings (114). Thus, NIH conducts a number of activities in addition to NLM activities noted in the previous section. The consensus development conferences and subsequent dissemination of their proceedings, sponsored by OMAR, is the program most directly related to the targeted transfer of technologies. It has already been discussed. In addition, the various institutes sponsor over 100 meetings annually for practicing physicians (53). The Office of Communications, in its annual list of publications (54), targets publications of particular interest to health professionals. And the Lister-Hill National Center for Biomedical Communications (a division of NLM) conducts and supports a continuing research program on the effectiveness and efficiency of biomedical communications.

Dissemination to the Public

In 1977, it was reported that the constituent units of NIH received about 1,500 public inquiries each working day. About 80 percent of those requests came from members of the general public and concerned specific disease problems (54). The volume of requests is even larger today. In response to public as well as congressional pressure, NIH continues to increase its dissemination to the public. The activities are numerous; they include targeting publications in the annual publications list to the general public, supplying audiovisual materials to over 2,000 radio stations and over 700 television stations, preparing instructional films, releasing news briefs, and sponsoring disease-specific public information centers such as the National Digestive Diseases Education and Information Center.

Technology Transfer to Industry

For medical technologies that are physical objects—drugs and devices—the technology transfer process involves industry. It is industry that actually produces and markets the technologies, thereby influencing their application in clinical practice. In many cases, the bulk of the transfer process occurs within the drug and medical device companies, from applied research to technology creation and development, through evaluation, to production and distribution. In these cases, the basic knowledge utilized in the company's applied research is often transferred from an NIH-sponsored program. The transfer mechanism is usually scientist-to-scientist communication through the professional literature or at professional meetings.

In other instances, however, the technology is developed and perhaps evaluated under NIH auspices. It is transferred to industry, then, much later in its lifecycle. Recently, there has been considerable interest within NIH and within Congress on this aspect of technology transfer (58).

Collaborative programs with industry have long been viewed by other agencies as a mechanism to facilitate the transfer process. Indeed, the National Aeronautics and Space Administration recognized early on that involving industry early in the teachnology development process would increase the likelihood that the technology would be produced. And in the field of technologies for disabled people, the National Institute for Handicapped Research has begun similar relationships with industry.

NIH, with its more recent commitment to knowledge application in addition to knowledge development, is relatively new in its agencywide interest in relationships with industry. For some time, Congress and others have been concerned about the commercial application of useful biomedical research findings. More recently, rela-

tionships with industry are expanding because of budget constraints. There are those, mostly within the government, that hope that the drug and device industries can pick up forthcoming cuts in biomedical research budgets. Pharmaceutical industry representatives, however, have stated that, although they can continue to fund "some areas" of biomedical research, they "can't pick up the massive slack" in available funds (21). Furthermore, relationships with industry are growing due to the clear commercial value in applications from basic science fields where there has been no precedent for profit (e.g., genetic engineering).

Industry patents and licenses are very important aspects of the transfer process. NIH is quite active in this regard, with approximately 370 patents licensed to industry.

The Advisory Committee to the Director of NIH has had as a priority for 1981 the relationship between NIH and industry. This priority continues today. Issues of concern include the following:

- how patent rights are allocated;
- how patent royalties are allocated—among scientists and their university, among universities and industry—and whether the government can recoup some of its investment in research;
- whether a longer period of patent protection and licensing is needed;
- how and when the government should invoke its march-in rights, the right to revoke a university's patent license if the license is not properly handled;
- what the best model for patent administration at universities is; and,
- what the impacts of patenting on the now-open system of communications in biomedical sciences will be.

Training

Since the objective of training programs at NIH is to produce more and better biomedical researchers, these activities do not have a direct impact on the technology transfer process. In several ways, however, they do affect the process indirectly. First, training funds develop the personnel resources to develop and evaluate technologies. This effect is most important to targeted technology transfer when the reseachers are trained in conducting evaluative studies to prevent the premature diffusion of untested technologies into clinical practice.

Second, when training is conducted at the specialized centers funded by NIH, such as the Diabetes Research and Training Centers, there is a formal combination of the training and technology transfer functions. The combination assists in current transfer and orients the trainees to develop similar programs of their own in the future. Finally, since much of the training occurs in institutions associated with clinical practice, interaction between the researcher trainees and the health professionals can allow for informal technology transfer.

Table 13 shows training grant appropriations by funding component from 1950 to 1980. From 1950 to 1967, the increases in funds were large, and the next period, until 1976, was one of fluctuation. Regulations issued under the National Research Service Award Act of 1974 in 1975 directed that awards could be made only in fields determined to be in need of research personnel; these regulations were partially responsible for the drop in 1976. Since that time, increases have been steady, particularly for the larger institutes. Thus, the problem of instability cited in 1976 by a congressional investigation of NIH (114) and the President's Biomedical Research Panel (97) was somewhat alleviated. Recent budget cuts are likely to affect stability.

Table 13.—Training Grant Appropriations by Funding Component, Fiscal Years 1950-80 (amounts in thousands of dollars)

Fiscal Year	GRS-NIH	NCI	NIMH	NHLBI	NIDR	NIAMDD	NIAID	NINCDS	NICHD	NIGMS	NIEHS	NIA*	NEI*	RR*	Total
															6,415
1950		2,625	2,956	834											6,652
1951		2,415	3,349	888											7,392
1952	86	2,415	4,000	891											8,184
1953	86	2,725	3,750	1,623											10,813
1954		2,855	4,176	3,028		250		504							11,051
1955		2,725	4,310	2,762		250		1,004							14,502
1956		2,725	5,885	3,142		950		1,800							28,075
1957	500	4,675	12,000	4,400	500	1,650		4,150							32,932
1958	500	4,725	14,000	5,135	500	2,450	650	4,972							49,902
1959	6,040	6,050	18,213	7,152	450	4,435	1,787	5,775							75,037
1960	13,040	7,205	26,206	8,679	1,100	6,298	3,621	8,888							110,000
1961	27,000	7,055	39,470	11,970	2,965	8,300	4,790	8,450							118,506
1962	31,000	9,055	34,856	13,104	4,791	10,300	5,400	10,000							154,139
1963	35,442	13,470	49,373	16,000	5,853	13,034	7,200	13,767							172,602
1964	35,682	12,482	65,168	14,801	4,759	13,220	7,966	14,382	[1]4,142						181,311
1965	37,182	9,000	73,213	14,984	4,708	13,690	8,239	14,751	5,544						209,896
1966		10,900	86,231	17,228	5,203	14,206	9,059	17,757	7,937	41,375					224,486
1967	250	11,068	94,448	17,525	5,248	14,857	9,103	18,633	9,619	43,735					138,806
1968	318	11,350	[2]	17,696	5,469	15,706	9,251	18,780	9,762	45,729	4,745				141,390
1969	326	11,641		18,150	5,609	16,109	9,488	19,262	10,012	46,901	3,892				146,469
1970	352	11,941		19,006	5,495	17,454	8,972	17,950	9,892	48,477	3,617		3,313		132,322
1971	[3]	10,774		17,643	5,206	15,072	8,972	14,300	10,142	43,746	3,117		2,998	352	145,325
1972		[4]16,474		18,701	5,582	15,976	9,457	15,158	10,751	46,371	3,304		3,178	373	148,795
1973[5]		16,750		19,343	5,270	15,072	8,982	16,324	11,598	47,511	4,131		3,398	416	126,253
1974[6]		13,742		16,069	5,515	12,312	7,933	16,516	8,552	39,247	2,900		3,056	391	120,274
1975		17,097		14,515	3,692	10,078	5,351	10,310	6,688	44,940	2,915	1,156	3,194	388	87,915
1976		12,868		11,839	3,235	1,247	4,537	4,006	6,644	37,599	1,453	1,133	3,194	160	106,551
1977		15,541		17,733	3,309	7,234	5,786	2,450	5,877	40,988	3,106	1,829	2,387	411	114,904
1978		15,191		19,321	3,219	12,587	5,556	3,059	6,097	41,580	4,036	1,856	1,990	412	121,919
1979[7]		17,110		19,098	2,780	12,663	5,875	3,584	8,370	42,371	4,293	1,854	3,452	469	145,936
1980[8]		22,901		27,622	3,487	18,123	7,097	3,854	8,342	42,092	6,121	2,170	3,530	597	

[1] Derived by transfers from other NIH appropriations as authorized by Congress.

[2] Transferred to HSMHA July 1, 1967.

[3] GR & S discontinued. Research Resources appropriation established.

[4] Includes portions of $100,000,000 Cancer Conquest Program and $40,000,000 supplemental.

[5] Formerly a part of the Neurology Institute.

[6] No appropriation bill signed in 1973. Figures are based on the continuing resolution.

[7] Reserve legislated by P.L. 93-192 not rescinded.

[8] Formerly a part of NICHD.

* Authorized by P.L. 95-482 (Continuing Resolution).

[9] No enacted appropriations, authorized under continuing resolution.

SOURCE: National Institutes of Health.

Chapter 6

The National Cancer Institute

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Chapter 6

The National Cancer Institute

INTRODUCTION

In 1979, cancer killed more than 400,000 Americans (47) and 815,000 new serious cancers were diagnosed (1) (see table 14). Over 3 million Americans alive today have had a diagnosed cancer. Cancer accounts for about 20 percent of total U.S. mortality, second only to heart diseases, which are responsible for about 38 percent of deaths.

Cancer has a major impact on the Nation's economy, both from the personal costs of treatment and lost income, and from public expenditures for screening programs, public education, and cancer research. In 1977, the most recent year for which information is available, direct costs for all cancers, including hospital care and physicians' services, amounted to about 7 percent of these costs for all illness (33). Indirect costs, based on a lost earnings approach (discounted at 6 percent), amounted to approximately 19 percent of total indirect costs (33). The fiscal year 1982 budget for the National Cancer Institute (NCI) is $986 million.

The costs of cancer are not exclusively economic. Social costs have taken on increasing prominence in recent years, and include more than the obvious pain and suffering of the victim. Relatives and friends of victims and caregivers may suffer direct consequences of the victim's morbidity and mortality. Social isolation, economic dependence, lost personal and business opportunities, and many undesirable alterations in lifestyle are inevitable. Serious emotional and psychological problems requiring professional attention are not uncommon among victims and their family members, often producing irreversible changes in family structure and relationships.

A common measure of disease impact is the number of years of life lost due to premature mortality. This index takes into account both the number of deaths and the age at which people die. Therefore, the death of a younger person will contribute more person-years lost than will the death of a person who is closer to having

Table 14.—Estimated New Cancer Cases and Deaths by Sex for Major Sites, 1981

	Total cases		Total deaths		Females				Males			
					Cases		Deaths		Cases		Deaths	
Site	Number	Percent of total	Number	Percent of total	Number	Percent of total	Number	Percent of total	Number	Percent of total	Number	Percent of total
Lung	122,000	15.0	105,000	25.0	34,000	8.3	28,000	14.5	88,000	21.8	77,000	33.8
Colon-rectum	120,000	14.7	54,900	13.1	62,000	15.0	28,700	14.9	58,000	14.4	26,200	11.5
Breast	110,900	13.6	37,100	8.8	110,000	26.7	36,800	19.1	900	0.2	300	0.1
Prostate	70,000	8.6	22,700	5.4	—	—	—	—	70,000	17.4	22,700	10.0
Uterus	54,000[a]	6.6	10,300	2.5	54,000	13.1	10,300	5.4	—	—	—	—
Urinary	54,600	6.7	18,700	4.5	16,600	4.0	6,500	3.4	38,000	9.4	12,200	5.4
Oral (buccal cavity and pharynx)	26,600	3.3	9,150	2.2	8,200	2.0	2,850	1.5	18,400	4.6	6,300	2.8
Pancreas	24,200	3.0	22,000	5.2	11,500	2.8	10,500	5.5	12,700	3.2	11,500	5.1
Leukemia	23,400	2.9	15,900	3.8	10,400	2.5	7,000	3.6	13,000	3.2	8,900	3.9
Ovary	18,000	2.2	11,400	2.7	18,000	4.4	11,400	5.9	—	—	—	—
Skin	14,300[b]	1.8	6,700	1.6	7,300	1.8	2,700	1.4	7,000	1.7	4,000	1.8
All others	177,000	21.7	106,150	25.3	80,000	19.4	47,750	24.8	97,000	24.1	58,400	25.7
Total	815,000		420,000		412,000		192,500		403,000		227,500	

[a]Invasive cancer only.
[b]Melanoma only.

NOTE: Estimates of new cancer cases and deaths are offered as a rough guide and should not be regarded as definitive.

SOURCE: Office of Technology Assessment, 1981 from American Cancer Society data.

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lived to full life expectancy. Cancer accounted for approximately 19 percent of all deaths in 1975, and about 16 percent of all years of life lost (104), indicating that the average age of those who die from cancer is greater than the average age of those who die from the aggregate of all other causes of death.

The importance of cancer in U.S. policies about disease is illustrated by the attention focused on cancer research. NCI, established in 1937, was the first institute of the U.S. Public Health Service to be devoted to a single disease. Initially a freestanding institute, it was incorporated into the National Institutes of Health (NIH) which was organized in the 1940's. In 1971, 34 years after NCI's establishment, an intensive effort was mounted in Congress to separate NCI from NIH and to establish a National Cancer Authority.

While the National Cancer Act of 1971 was unsuccessful in establishing a new authority, it elevated NCI to bureau status, a higher organizational level than any other institute at NIH until the National Heart, Lung, and Blood Institute (NHLBI) was also made a bureau. The act also resulted in remarkable growth at NCI (see addendum A).

This chapter was developed by a review of selected literature and through a number of telephone interviews of experts. The questions that were mailed to the experts and a list of the addressees are included as addenda B and C. OTA staff talked with 22 individuals on the list and to another group of about 15 experts who were suggested by those on the list.

Throughout this chapter, attribution to named individuals refers only to published papers or quotes from news sources. Information obtained during conversations with experts is so identified, but no specific attributions are made. Care has been taken to make plain those cases in which an opinion was heard from more than one person as opposed to only one person.

CANCER MORTALITY AND INCIDENCE

Nationwide mortality data are used to answer questions about the number of deaths caused by cancer in the United States. Without doubt, the number of Americans dying from cancer has increased during the last century. Paradoxically, a major part of this increase has resulted from improvements in public health and medical care. In years past, infectious diseases killed large numbers of people in infancy and during childhood. Now that advances in health care have softened the impact of those diseases, many more people live to old ages when cancer causes significant mortality.

Deaths from cancer are not evenly distributed among all body sites; the lung, colon, and breast account for over 40 percent of the total (see table 14). Discussion of cancer rates at particular body sites is more revealing than discussion of overall trends which mask changes at individual sites. Moreover, some cancer-causing substances act at specific sites, and more information about opportunities for prevention is obtained from the analysis of trends at particular sites. Likewise, survival rates and improvements in treatment vary at different anatomical sites.

The trend that has dominated all others over the past 50 years is the increase in lung cancer mortality, largely a result of the widespread adoption of cigarette smoking earlier in this century. Male lung cancer rates have been rising steadily for at least half a century. Female lung cancer rates started to rise about 25 years ago and are now increasing rapidly. All other changes are small in comparison with the large increases in smoking-related cancers, although the decreases in cancer of the stomach and uterus are also important.

Currently, there is a general tendency for the rates of change at each cancer site to be slightly more favorable for people under 65 than for those over 65: If the site-specific rate for all ages is increasing, it is increasing at a slower pace among the younger group; if the rate is decreasing, the decrease is more pronounced in those under 65. Two clear exceptions stand out. First,

skin cancer is increasing much more rapidly among males under 65 than among those over 65. Second, mortality rates of brain tumors appear to be moving in opposite directions; despite falling death rates in middle age, there are large increases in old age, perhaps because of better diagnosis for older people which improves the efficiency of case reporting.

If attention is restricted to those younger than 65, for almost all types of cancer except those strongly affected by smoking (cancers of the respiratory and upper digestive tracts), the most recent trends in mortality are downward. The chief exceptions are pancreatic cancer in women, and melanoma in whites of both sexes.

Incidence rates differ from mortality rates because not all people who contract cancer die of it. Rates are calculated by relating the number of cases or deaths to the "population at risk" of either contracting cancer or dying from the disease. "Crude rates" are the total number of cases or deaths divided by the total population. Crude rates are affected by changes in the age structure of the population, i.e., the fact that there are more older people in the population today, and hence more people contracting and dying of cancer, means that the crude rates will increase. All of the overall comparisons in this report are based on rates "age-standardized" to the composition of the population determined in the 1970 census. Changes in these rates occur because of changes in the risk of cancer among people of a given age; increases or decreases in the proportion of old people in the population do not affect age-standardized rates. When a figure or comparison refers to a specific age class, the rates are based on the cases or deaths as a proportion of the total number of people in that class.

Apart from whether or not cancer rates are changing, many variables contribute to the greater prominence accorded the disease today as compared to even a few decades ago. A major factor in its emergence is the sharp decrease in deaths from infectious diseases such as tuberculosis, dysentery, and diphtheria over the past 100 years. Before the mid-19th century, these diseases killed far more people than did chronic diseases. General improvements in living conditions, public sanitation, and nutrition began to reduce the rates of infectious diseases, and the decline was hastened by advances in biology and medicine early in the 20th century.

As the decades passed, these improvements have shifted the age structure of the population upward; as a result, there is a larger proportion of people over 65. Cancer risks have always been 10 or 100 times greater among older people than among younger people. The change in age structure increases the actual number of cases and deaths (crude incidence and crude mortality) but not necessarily the age-standardized cancer rates.

Second, cancer has become *relatively* more common as a cause of death because of the prevention or cure of other diseases. This phenomenon is illustrated by the mortality data for females in 1935 and 1975 (see table 15). Nonrespiratory cancer death rates decreased substantially, but the death rates from all other causes decreased even more. Therefore, the *percentage* of female deaths attributable to nonrespiratory cancer was greater in 1975 than 40 years earlier, even though female nonrespiratory cancer deaths had declined during that period.

Third, many cancers, which might previously have gone unnoticed or unreported, are now

Table 15.—Death Rates per 1,000 Females, 1935 and 1975

Year	All causes except cancer	All nonrespiratory cancers	Respiratory tract cancers	All causes
1935 (1933-37)	11.92[a] (87.6%)[b]	1.65 (12.1%)	0.03 (0.2%)	13.60 (100%)
1975 (1973-77)	4.96 (78.8%)	1.17 (18.6%)	16 (2.5%)	6.29 (100%)

[a]All ages, age-standardized to the U.S. 1970 census population.
[b]Percentage of rate for all causes.

SOURCE: Office of Technology Assessment, 1981.

diagnosed both during medical treatment and in death certification. This change is especially pronounced among the elderly who today receive more medical attention than in premedicare years.

Finally, cancer is discussed more openly in the media and among friends and relatives of cancer patients; public figures no longer try to conceal their diseases. Previously, such matters were often hushed up and the diagnosis perhaps withheld even from the victim. The jump in the reported incidence of breast cancer in 1974 and 1975 is attributed to the publicity surrounding Happy Rockefeller's and Betty Ford's breast cancer surgery. Greater public awareness led to more women being examined, the detection of more cancers, and more accurate reporting, but the reported increase in those years is not considered to reflect a real increase in incidence.

REDUCING CANCER'S IMPACT

There are three approaches to reducing cancer's impact: prevention, the ultimate goal; earlier detection; and improved treatment. The general consensus that most cancers are caused by extrinsic forces (86) has led to the view that many cancers are preventable. Estimates of theoretically preventable cancers have reached as high as 90 percent of the total, though the practical limits undoubtedly will be lower.

Once identified, exposures to carcinogens may be reduced either through voluntary or regulatory methods. There has been one notable success among efforts to influence personal behavior—the reduction in cigarette smoking among adults. The decrease is most notable among adult males, and can confidently be attributed to the publicity and attention given to adverse health effects of tobacco. Between 1965 and 1979, the proportion of adult male smokers dropped from 51 to 37 percent. The decline among women over the same period was much smaller, from 33 to 28 percent.

Antismoking efforts on the part of NCI and other organizations, notably the American Cancer Society, are considered partially successful. However, many people still smoke and smoking initiation rates may still be rising in teenage girls. A number of the people OTA spoke with, in basic and applied research and administration, expressed the opinion that, because this is one area in which there is virtually no serious disagreement about the cause of a major cancer, continued smoking is the greatest failure in cancer control.

It is generally believed that American eating habits are healthier than they were early in this century and that some of the changes, though not specifically identified, have spurred the decrease in stomach cancer rates. Future cancer-reducing changes in dietary habits may result from research into mechanisms by which dietary components cause or prevent cancers, or from epidemiologic observations of associations between dietary components and cancers.

In the last year, NCI approved its first large-scale "chemoprevention trial," from the Division of Resources, Centers, and Community Activities (DRCCA), based on the hypothesis that beta-carotene, the precursor of vitamin A, reduces cancer rates for at least some sites. The study is being funded jointly by NCI and NHLBI, and will also test the effects of aspirin as a prophylaxis for heart disease.

Early detection of cancers may improve overall survival rates when efficacious treatment is available. Localized cancers detected before they metastasize can be excised completely, leaving the patient with an excellent chance for survival. The proportion of cancers detected at "early" v. "late" stages has increased over time. For example, between the early 1950's and the late 1960's, the proportion of prostate cancers diagnosed as "localized" increased from 48 to 63 percent. Over that period, the 5-year relative survival for prostate cancer climbed from 43 to 57 percent. The overall relative survival rate is the ratio of the observed survival rate of the treated group to the expected survival rate for persons of the

same age, sex, and race in the general population. Three elements may contribute to the apparent improvement. Part of the improvement may be artifactual and result from detecting and reporting less serious tumors in the late 1960's, that, had they occurred in the early 1950's, would not have been reported. Some of the improvement probably resulted from better treatment. However, a major component of the gain resulted from detection of tumors at earlier stages, when they could be more successfully treated (61). The same pattern has occurred in some, though not all, body sites.

Surgery, radiation therapy, and chemotherapy are the mainstays of cancer treatment. There have been advances in all three areas. Refinements have been made in surgery and in radiation therapy as technologies have improved. There have been no quantum leaps in surgery and radiation therapy at least since the 1950's. This is not necessarily a criticism of NCI, but a sign that perhaps, particularly for surgery, there are diminishing returns in efforts to improve survival. In particular, disseminated cancers cannot be treated by excision of all tumor cells. Improved surgical procedures generally emphasize doing less surgery with no loss of survival benefit, a move toward improved quality of cancer treatment.

Some "quantum leaps" have been made in chemotherapy, and in terms of treatment, this area still holds the greatest potential, particularly in integrating chemotherapy, surgery, and radiation into better treatment regimens. Chemotherapy has had a major impact on Hodgkins and non-Hodgkins lymphomas, childhood leukemias, testicular cancers, and osteogenic sarcoma, and choriocarcinoma. There is evidence that, in coming years, survival for certain groups of breast cancer patients may be improved by the use of postsurgery chemotherapy.

Presently, NCI (19) estimates that 46,000 patients yearly are helped by chemotherapy. Scientifically and medically, the successes represent promising advances. With longer followup periods, more studies might indicate substantial gains. However, because many people who receive the drugs (which are often accompanied by undesirable side effects) experience no substantial gain in life expectancy, concern about the use of chemotherapy has developed in some parts of the medical profession and in the minds of the public.

YARDSTICKS FOR MEASURING THE SUCCESS OF CANCER RESEARCH

The Cancer Control Program at NCI is mandated by the National Cancer Act (69). In addition to that program, the Cancer Centers Program and clinical trials of treatment regimens promote and facilitate technology transfer. The basic requirement of any technology transfer program is a scientific base of knowledge.

NCI research is directed at increasing knowledge about cancer; development, demonstration, and transfer activities, dependent on research, are aimed at reducing incidence and mortality.

Increases in Knowledge

In 1973, an Institute of Medicine (IOM) committee (44) suggested that the following avenues of research were likely to be fruitful in the years ahead: "DNA replication, the cell cycle, regulation of transcription, regulation of membrane assembly and function, cell differentiation, regulation of protein synthesis, and all aspects of cellular immunity."

The next paragraph cautioned, however, "The list should be regarded as flexible, subject to additions or changes depending on the progress of cancer biology itself."

Nine years later, in 1982, a number of experts contacted by OTA suggested areas of research most likely to yield important results. Often mentioned were recombinant DNA research, hybridomas and mononclonal antibodies, and better methods for risk assessment. None of

these were listed by the IOM committee. Although the basic discoveries about recombinant DNA were published in 1971, their impact had not been fully appreciated in early 1973; hybridomas were simply unknown; monoclonal antibodies a hypothesis. Risk assessment was little discussed and of little perceived importance.

A decade ago, understanding of the possible mechanisms by which genes regulate and control cells and how cells synthesize gene products was based on elegant experiments in bacteria and the viruses that infect them. The last 10 years have seen that some of those ideas have much less application to human cells than was expected. Although some scientists have claimed that they had inklings of the extraordinary differences between production of gene products in bacteria and mammals, those claims are dismissed. The new ideas about mammalian cells were forced on scientists by experimental results. At the same time, without the bacterial models as a baseline, little progress would have been made in understanding mammalian cells. Several experts who talked with OTA emphasized the importance of NCI's support of basic research, both intramural and extramural, in these discoveries.

These examples illustrate the impossibility of predicting the direction, results, and applicability of basic research. Basic knowledge about mechanisms important in cancer and in biology in general has increased greatly in the last decade, but the productive approaches of the last 10 years may not be the only ones to pay off in the years ahead.

There is no yardstick to hold up to basic research progress that is similar to the actuarial measurements of cancer incidence and mortality that are discussed below. The awards of Nobel Prizes and other trophies are in recognition of excellence, but they may come soon after or much after the important discoveries and they reward only a fraction of outstanding basic research. Scientists often describe progress in their own fields, but they face a difficult problem in coveying their excitement and approbation to more lay audiences. Experimental technicalities, laboratory jargon, arcane mathematical measures, immersion in a sea of details interfere with the expert's communication to others not so expert. (A refreshing contrast to those difficult-to-understand measures is provided by Lederberg (41). Even without these problems, some scientific concepts are difficult to understand. For many people, the most convincing evidence of the importance of basic biological research has been the formation of genetic engineering companies with large amounts of capital provided by financial organizations that have made a great deal of money in the past.

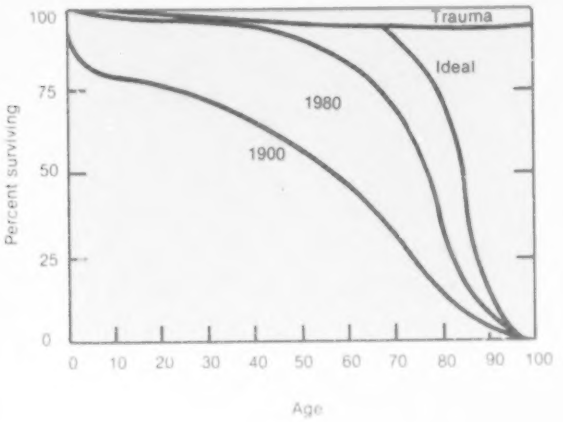
A measure of progress in basic research more directly related to cancer are the reports of experts who teach courses about cancer. The content of those courses has changed dramatically during the last decade. Such teachers rely on articles in recent scientific publications. Neither last year's notes nor textbooks are sufficiently current.

Reduced Mortality From Some Cancers

The ultimate desired effect of health research and development programs is longer lives and more disease-free years. Extending maximum human lifespans by many years seems unlikely, but extension of more people's lifespans to the biological limit seems attainable. The idea that humans' lifespans are fixed by some biological clock is discussed by Fries (22) and Fries and Crapo (23). Very, very few people live to ages much greater than 100; the percentage of centenarians in England's population has not increased since 1837 despite great changes in average life expectancy. Disappointingly, reports of people living to very great ages, 110 or more, are largely from less developed countries. The number of those reports varies directly with the illiteracy rate, and it is reasonable to conclude that these reports are the product of faulty recordkeeping.

Fries and his colleagues find that while there has been little change in the maximum expected lifespan, more and more people are living to or almost to what appears to be a maximum expected age (see fig. 3). The maximum expected age seems to be about 85, with a distribution of people dying within a few years of that age.

Figure 3.—Changes in the Percentage of People Living to Specified Ages, 1900 and 1980



The increasingly rectangular survival curve. About 80 percent ( ) of the difference between the 1900 curve and the ideal curve ( ) had been eliminated by 1980. Trauma is now the dominant cause of death in early life.

SOURCE: Fries, 1980.

Cancer accounts for about 20 percent of U.S. mortality (86). Despite that large percentage, eliminating cancer as a cause of death would have only a small effect on the average U.S. lifespan, because cancer is largely a disease of advanced age. About 90 percent of cancer deaths occur in persons over 65. While average life expectancy might be little affected by preventing cancer deaths, preventing cancer at whatever age improves the quality of life.

OTA's *Assessment of Technologies for Determining Cancer Risks From the Environment* (86) and Doll and Peto (20) discuss mortality rates from cancer. Significant decreases have been seen in mortality from some types of cancer—stomach, uterine cervix, lung cancer in men younger than 50 during the last two decades, and Hodgkin's disease, other lymphomas, and some childhood cancers.

The causes of the declines in the first two remain largely matters of speculation. Higher standards of living, more varied diets, and better food preservation techniques have been associated with decreases in stomach cancer mortality, which became noticeable in the 1930's and have continued. The downward trend in uterine cancer mortality over the past 50 years is a major factor contributing to the steady decrease in death rates from nonrespiratory cancers in females. Again, the causes are not clear, but improved personal hygiene associated with higher standards of living may be involved in the decrease. Decreases in uterine cancer mortality preceded the development and widespread introduction of cervical cytology screening for the disease by at least 25 years. The importance of the screens in the continuing decline is difficult to assess. In the case of stomach and uterine cancers, for poorly understood reasons, there have been decreases in incidence that are translated directly into decreased mortality.

The observed decreases in lung cancer incidence and mortality in young men are directly related to changes in smoking. Hodgkin's disease, other lymphomas, and some childhood cancers differ from the others; mortality from them has decreased because of better treatment and increased survival rates.

The examples of declining mortality from these cancers illustrate the two types of intervention that can reduce cancer mortality: reducing cancer incidence and improving treatment. The National Cancer Program Plan recognized the preferability of reducing incidence. Four of the seven objectives of the Plan focus on cancer cause and prevention (69).

Changes in Cancer Incidence

Recent years have seen much progress in identifying enviromental agents and personal behaviors that are associated with higher cancer risks. A thorough examination of epidemiologic studies of the occurrence of cancer in the United States (20,86) reaffirms the impression of many experts that, to a major extent, we have only clues about what causes cancer. The few positive exceptions, in which causes are clearly identified, are relatively well known—smoking, exposure to asbestos, radiation, sunlight, some chemicals, and some drugs. More typical of our level of knowledge is the case of food. Through various methods, a number of different estimates have been made that suggest that as much as 50 percent of all cancer is associated with elements

in the diet. This observation provides a tantalizing lead for further study, but so far few specifics are known (20,71,86). Finally, there are some cancers for which there are still no hypotheses about their causes.

As more specific knowledge is obtained and prevention activities are increased, measurements of their success in the general population will depend on obtaining reliable incidence data. Each new case of cancer, whether it is subsequently cured or results in death, is recorded in incidence data; mortality data record only deaths. As is described elsewhere (20,86), mortality data have been collected on a nationwide basis since 1933. No nationwide incidence data are collected. The NCI Surveillance, Epidemiology, and End Results (SEER) program now collects incidence data on about 10 percent of the U.S. population (see below).

Incidence data have been used in the recent past, 1980 and 1981, to support arguments that cancer is rapidly increasing in the U.S. population (112). The most recent summation of SEER data, released to the press in late 1981, does not support the idea of rapid increases in cancer occurrence at any major sites except lung.

Prevention, which precludes illness and the rigors associated with treatment, is highly desirable in cancer. Measuring the effects of prevention programs will require accurate, comparable incidence data collected from (probably) large segments of the population.

Changes in Survival

The third actuarial measure of success for the National Cancer Program are improvements in treating cancer as measured by more people surviving the disease. This measure, generally expressed as the percentage of newly diagnosed patients surviving 5 years after treatment, after adjustment for "normal" life expectancy, is called "5-year survival rates." These data have taken on more importance with recent announcements of treatment success from NCI. The most recent report from NCI (19) depends on incidence data collected by the SEER program.

One of the seven objectives of the National Cancer Program (16,44,69) was directed at treatment. As this chapter discusses, and is commonly agreed, NCI has emphasized treatment and curing cancers. To a major extent, this emphasis is understandable, because it offers opportunities to help people in need of care now. At the time of the National Cancer Program Plan's development, therapeutic advances were in hand and more were expected (28,64). Exploitation of those advances is certainly justified, but questions are raised about the balance being struck between treatment research activities and other research activities at NCI. An additional, tiger by the tail, reason for the emphasis on treatment is congressional pressure. As NCI lauds its treatment advances, the public, through Congress, demands access to them. In response, NCI bends more effort to treatment research and cancer control.

Cancer Treatment and Curing Cancer

At the time the National Cancer Act was being considered in 1970, the National Panel of Consultants on the Conquest of Cancer reported (28, quoted in 66).

> The cure rate for cancer is gradually improving. In 1930 we were able to cure only about 1 case in 5; today we cure 1 case in 3; and it is estimated that the cure rate could be brought close to 1 case in 2 by a better application of knowledge which exists today, i.e., detection at an earlier stage through the more widespread use of existing techniques (such as the Papanicolaou test for women and mammography), coupled with an extension to all citizens of the same quality of diagnosis and treatment now available at the best treatment centers.

The last part of this quote touches directly on cancer control, which includes efforts to move the best treatment from specialized centers to all citizens. Increased survival rates are the expected results from such efforts, and, in fact, by all measures, survival has increased, albeit not so much as expected in 1970.

Some of the reported improvements in cancer treatment survival have stemmed from general improvements in radiotherapy and surgery in

the post-World War II years. Improved radiotherapy and surgical techniques, better aseptic procedures, antibiotics, and better postoperative and supportive care have contributed to the improving cure rates.

Beginning somewhat later, and well underway by the late 1960's, chemotherapy has brought significant improvements to the treatment of some cancers. From a compassionate standpoint, these improvements, which were and are especially pronounced in the treatment of childhood cancers, are gratifying.

The triad of cancer treatments is completed by radiation therapy. A recent survey (108) shows that the presence of a radiation therapy unit is the second most important factor (after having an American College of Surgeons-approved program) in determining the number of cancer cases treated by a hospital.

The most encouraging projection about cure rates has been made by the NCI Director (19). From examination of data collected through the SEER program, he concludes that during the period 1975 to 1979, 46 percent of diagnosed cancers among whites and 45 percent among all races were "curable." A "more optimistic calculation from the same data results in a 50 percent 5-year survival for white patients and 49 percent for all races." To date, the cure rate for specific sites has not been published. Furthermore, this is the first calculation of survival rates using SEER data, and the reported rates may not be directly comparable to data collected earlier under other systems.

The American College of Surgeons has collected information about cancer cure in community hospitals. Upon presentation of appropriate information about a hospital's cancer treatment program, the American College of Surgeons will approve the program. Approved programs are found more frequently in larger hospitals: 14 percent of all acute-care hospitals have approved programs, and those contain 32 percent of hospital beds (see table 16). The approved hospitals treat a disproportionate number of cancer cases: 60 percent of all newly diagnosed cases are treated in the 14 percent of hospitals with American College of Surgeons-approved programs.

Estimated 5-year survival rates were reported from four types of hospitals (see table 17). The rates for community and university hospitals are quite similar; lung cancer remains intractable to treatment, and its higher frequency in the Veterans Administration (VA) and military hospitals

Table 16.—Distribution of Commission on Cancer of the American College of Surgeons-Approved Hospital Cancer Programs According to the Size of Community Hospitals in the United States

Bed size of hospital	Number of hospitals in United States	Number of approved cancer programs
501 and over	385	216 (56%)
301-500	717	317 (44%)
101-300	2,152	359 (16%)
Under 100	3,285	51 (>1%)
Totals	6,539	943 (14%)

SOURCE: Smart, 1981

Table 17.—Five-Year Estimated Survival Rates After Treatment of Cancer in Community, University, Veterans Administration and Military Hospitals, and Children's Hospitals

	Community	University	VA and military	Childrens
Number of hospitals	555 (84%)	28 (4%)	67 (10%)	9 (2%)
Number of cancers	1,420,213 (82%)	196,483 (11%)	114,639 (7%)	14,292 (1%)
5-year estimated survival	37%	36%	30%	45%
Most frequent cancer sites:	Breast	Lung	Lung	Leukemia
	Lung	Breast	Head and neck	CNS
	Colorectal	Cervix	Prostate	Soft tissue
	Prostate	Colorectal	Colorectal	Bone
	Cervix	Lymphoma	Bladder	Kidney

SOURCE: Smart, 1981

contributes to the lower survival rates in those institutions.

Overall survival rates from "cancer," which includes about 100 different diseases, are not so informative as rates from particular cancers. Smart (108) has compared 5-year survival rates found in whites by NCI in 1965-69 to those found in the American College of Surgeons' survey over the period 1973-79 (see table 18). Improvements are reported for each cancer. Smart cautions against too detailed comparisons between the two sets of data, because the data were collected using different systems during the two time periods. A more meaningful comparison can be drawn by examining survival data collected in a standard method by NCI during two different time periods. Inspection of those data (table 18) show improvements in survival from cancer at almost every site, in both races and sexes. Survival for Hodgkin's disease and acute lymphocytic leukemia have shown the greatest improvements, and stomach, pancreas, and lung the least. Further improvements can be expected when details of more recent data collected by the SEER program are published.

A decade after the estimate that 50 percent of cancers might be curable, the 5-year survival rate remains below that figure in the American

Table 18.—Comparison of Five-Year Relative Survival Rates From NCI Studies in 1960-63 and 1970-73

Cancer site	White males		White females		Black males		Black females	
	1960-1963	1970-1973	1960-1963	1970-1973	1960-1963	1970-1973	1960-1963	1970-1973
Stomach	10	12	13	14	5	15	14	10
Colon	42	47	44	50	32	36	35	38
Rectum	36	43	41	48	28	20	27	40
Pancreas	1	2	2	2	0	0	3	3
Lung	7	9	11	14	5	6	6	10
Melanoma	51	62	68	75	*	*	*	*
Breast	—	—	63	68	—	—	46	51
Uterine cervix	—	—	58	64	—	—	47	61
Uterine corpus	—	—	73	81	—	—	31	44
Ovary	—	—	32	36	—	—	32	32
Prostate	50	63	—	—	35	55	—	—
Bladder	53	61	53	60	24	38	24	27
Hodgkin's disease	34	66	48	69	*	*	*	*
Acute lymphocytic leukemia	4	27	3	29	*	*	*	*

*Number of patients too small to yield reliable rates.

SOURCE: National Cancer Institute, 1981.

College of Surgeons' study (108). In fact, the one in three cure rate estimated in 1970 is close to that seen today in that review. NCI's own estimate of cure rates is higher, 46 to 50 percent, and it approaches the goal of curing one case in two. It is likely that more cancers will be cured as improvements move from NCI to the community. Importantly, of course, within the limits of the improvements that have been made, lives have been spared and the side effects of treatment have been reduced. NCI has contributed to these important advances.

Several experts contacted by OTA suggested that adjuvant chemotherapy (drugs used in association with other treatments) has already contributed to improved cure rates, and more improvements are expected. Not unexpectedly, experts with a background in clinical research and applications expressed enthusiasm for curative changes and urged continued emphasis on clinical research. Other people caution that some of the reported improvements may be artifactual because of changes in reporting methods and that additional incremental improvements may be small.

The proper balance between treatment research and other research efforts is continuously debated. Whatever the proper balance, the impression left by the following sentence in the 1981 Director's Report (68) suggests that it has not yet been struck: "Mortality results not only from failure to treat adequately but also from failure to prevent disease." Many observers would order the failures differently.

Surveillance, Epidemiology, and End Results Program

Measurements of cancer incidence and survival rates depend on data collected by the SEER program. SEER is the first nationally coordinated, continuous, population-based incidence registration system and was begun in 1973 by NCI. SEER is, in part, an expanded sequel to the successful End Results Program.

In SEER areas, attempts are made to ascertain every primary cancer, excluding nonmelanoma skin cancer. All information pertaining to a case is consolidated into one record to facilitate followup and to correlate survival data with treatment, age, and other variables.

SEER program data are collected from about 10 percent of the total population, but the geographical regions covered by the SEER program do not closely represent the demographic makeup of the entire country. A SEER report for the first 4 years of operation compared the demographic characteristics of the population with the total U.S. population (65):

> . . . the participants . . . are fairly representative with respect to age. Blacks are somewhat underrepresented, while other nonwhite populations (Chinese, Japanese, Hawaiians, and American Indians) are somewhat overrepresented. Rural populations (especially rural blacks) are also underrepresented.

The current SEER program costs about $10 million annually out of the total NCI budget of about $1 billion. Expanding the program to collect more representative data and to validate data more thoroughly would cost more money and would also require cooperation of additional local medical organizations to establish new SEER data collection areas. Balanced against these costs are opportunities to gather incidence and survival data representative of the whole country and to learn more about cancer in the U.S. population.

The two basic SEER program functions—collecting data on incidence and on mortality— are complementary, and baselines have been established for both measures. However, because the system is so young at this time, little can be said about trends in either.

The SEER program plays another important role in providing information on cancer cases to be used in epidemiologic case-control studies. The purpose of such studies is generally the identification of possible causative factors for a particular type of cancer. The largest cancer case-control study undertaken by the Federal Government, a study of about 3,000 of bladder cancer uses, relies on cases identified by SEER. Data

from the bladder cancer study are still being analyzed, but already the analysis has produced information of great value to cancer researchers involved in primary cancer prevention. Assembling the cases would have been more difficult and expensive if any other method had been used for case-finding.

TECHNOLOGY TRANSFER ACTIVITIES

Clinical Trials

Clinical trials in cancer research have been used mainly for testing anticancer drugs at varying dose levels and in various combinations. Multimodality studies, testing combinations of surgery, radiation therapy, and chemotherapy are also evaluated in clinical trials. Additionally, clinical trials have an important role in technology transfer; they demonstrate the usefulness of treatment regimens, and, increasingly, they involve community physicians in clinical research.

In cancer, perhaps more so than in other diseases, the results of chemotherapy are extremely variable. Patients with cancers at each stage—local, regional or advanced—of the approximately 100 types of cancer may react quite differently. This means that large numbers of patients are needed to get meaningful results in a treatment trial. A test of a promising therapy might require several hundred patients, which might require 2 to 4 years of recruitment, even with multi-institution cooperation. At least 4 to 5 years of followup are necessary before a reasonable evaluation can be made. Unfortunately, nothing can be done at this time to change those numbers. The nature of the disease, the state of the art of treatment, and statistical probability dictate the limits.

A trial as described above represents a large investment of money, and it does not promise any fast answers. A number of people expressed to OTA the notion that NCI has felt pressure to produce results in a short time and, perhaps as a result of that, some clinical trials funded either directly or indirectly by NCI are short-term, with few patients and with little chance of producing reliable results. These generally represent trials carried out in single institutions. Multi-institution trials generally have larger numbers of patients and go through the formal review process, and, overall, meet higher standards than single-institution trials.

In 1979, a subcommittee of the Board of Scientific Counselors of the Division of Cancer Treatment conducted a review of the large-scale cancer therapeutic Clinical Trials Program (67). The subcommittee found that, "While the clinical trials process has been good, the subcommittee is of the opinion that it can be further improved in preparation for the clinical cancer research era of the 1980's." The subcommittee's review resulted in four major recommendations (67):

1. We recommend that a new study section be established to review individual investigator initiated clinical cancer research.
2. In accord with federal guidelines, a cooperative agreement should be negotiated between the Division of Cancer Treatment (DCT), NCI and the Cooperative Oncology Groups.
3. We recommend that funds from the Cancer Control Program be transferred to DCT for cooperative group activities in support of groupwide Phase III protocols. . . . It is essential that the peer review process for award of Cancer Control funds be the same as that applied to the groups as a whole.
4. We recommend that DCT continue and increase its efforts toward information exchange on cancer therapy evaluation. It should be extended so that it includes more input and return to participants in clinical program projects (PO1's) as well as to the cooperative clinical trials groups. . . . we recommend that additional government positions be created in DCT to permit expansion of the Cancer Therapy Evaluation Program.

Each of these four recommendations was addressed by DCT in their September 1980 document, "Future Direction in Extramural Clinical Trials." The responses to each are summarized as follows (66):

1. The Division of Research Grants (DRG) set up a series of ad hoc study sections to review clinical research proposals. At the time of the response, NCI's policy was that, "If the results of this experimental group study section are satisfactory, a permanent study section will be considered by DRG." According to recent information from NCI,* "Data accumulated in the course of four such ad hoc reviews of RO1 applications for support of clinical research projects suggested that these 'clinically oriented' review groups disapproved somewhat more proposals and voted, on the average, somewhat higher (worse) priority scores than had been observed when a similar body of applications were reviewed by the most appropriate chartered DRG study section."
2. "DCT plans to convert the cooperative group program (RO1 grants), the Lung Cancer Study Group (contract), the Gastrointestinal Tumor Study Group (contract), the Brain Tumor Study Group (contract), the Melanoma Tumor Study Group (contract), the Head and Neck Cancer Study Group (contract), and the Parenteral Nutrition contracts, Phase II GI contracts, Large Bowel contracts, and the Breast contracts to the cooperative agreement mechanism. These conversions will be implemented within the next year . . . . All clinical trials research supported under cooperative agreements will be reviewed by a single type of review body." According to recent information from NCI,* the plan currently underway involves the formation of review branch, "the specific function of which will be to assess the scientific merit of applications of this type requesting support of clinical cooperative groups."
3. "Plans for redistribution of control moneys are being actively discussed with the DRCCA."
4. "Expansion of the Cancer Therapy Evaluation Program (CTEP) staff is being evaluated at present. Funding and position constraints will require careful consideration in making decisions regarding CTEP staff size."

*NCI, personal communication, Mar. 10, 1982.

The move to convert most clinical trial research to the cooperative agreement mechanism appears to be the most significant change to come from this review and DCT response. NCI is in the process of converting the currently grant-supported clinical cooperative groups to the cooperative agreement mechanism, after which the contract-supported research will be converted. NCI sees several advantages to this mechanism, relating basically to increased input into and control of clinical trials research. The cooperative agreement mechanism as defined in the 1977 Federal Grant and Cooperative Agreement Act is appropriate for funding trials, because "the purpose of the relationship is the same as that of a grant, but the Federal Government anticipates substantial involvement with the recipient during the course of the activity" (66).

The main difference for current grantees is that the terms of the cooperative agreements award will specify "substantial Government involvement," which is absent from grant awards. For current contractors, the application and funding process will change, and "scientific and administrative direction by NCI staff for these groups will be diminished" (66). Some of the specific terms of "substantial Government involvement" include increased participation in protocol design, protocol review, quality control, data management, the right to terminate a study, and an increased role in investigational drug management.

NCI states that "both contractors and grantees should have to make only minimal adjustments in their current operating procedures" as a result of the conversion to cooperative agreements, and that the conversion simply makes formal a relationship that already exists (66). The conversion has not gone as expeditiously as expected, however, and agreements may not have been worked out with all of the cooperative groups. One of the people with whom OTA spoke expressed concern over increased control by NCI over clinical research, particularly the provision that NCI retain the right to terminate a trial.

That decision, he said, should be made by the investigators. A number of other points of concern about clinical trials were expressed by the individuals with whom OTA spoke; these are described in the remainder of this section.

Many cancer clinical trials are carried out in single institutions with fewer than 50 patients, and many are not randomized trials. An added concern with small single-institution studies is that there may be insufficient review of the study protocol or the data analysis. Unless the institution has a data collection system in place, data management may be poor, leading to a poor analysis. These concerns are particularly directed at trials funded only indirectly by NCI, for example, through clinical centers, in which case the study protocol need not have gone through peer review. Nevertheless, NCI has direct involvement in most trials, at least in supplying the necessary drugs.

The opinion was expressed about clinical trials, as about other aspects of NCI-supported research, that funding reviews occur at too short intervals. The cooperative groups have been reviewed every 3 years or so, barely the recruitment period of a medium to large clinical trial. The quest for results in a short time has not been reconciled with the nature of the disease, in which meaningful results can only be measured over the long term.

It is estimated that between 6,000 and 10,000 clinical trials are currently being carried out worldwide, most including a small number of patients. Statistical analysis shows that several hundred trials that are in truth negative will appear to be positive based on probability alone (120). It is impossible in these cases to distinguish between a true positive and a false positive. Because clinical trials in cancer have a fairly low probability of success to begin with, we may in fact be overwhelmed by false positives, but there is no way of knowing this. One step that could be taken to remedy this is to carry out confirmatory studies for therapies that are positive in one clinical trial. One of the experts with whom OTA spoke criticized NCI for giving low priority to funding such studies because they are considered to be duplicative. In light of the admittedly low payoff of most cancer clinical trials, and the importance of introducing only beneficial therapies into practice, this policy might be reexamined.

NCI has recognized the need for large-scale trials for many years and has made improvements in facilitating them. Funding of the Cooperative Oncology Groups Outreach Program was a step forward in getting the community hospitals involved, and the incipient Community Clinical Oncology Program (CCOP) is another (see below). However, the problem is far from solved. At any time, there will undoubtedly be a number of trials going on of treatment of any given type of cancer "competing" for patients. One NCI official said that NCI has failed to act toward supporting the truly high-priority trials. He felt that NCI could be more intrusive in channeling patients nationwide into such studies. This may not be welcomed by all members of the clinical research community, however, who feel that grant-supported investigators should be more and not less free of NCI control.

A shortcoming of some clinical research in cancer today is the lack of biological basis for carrying out studies. Often, a clinical trial is just another combination of existing therapies, or a new dose level, and the only outcome measured is the effect on the tumor. This is, of course, the ultimate measure, and no trial should be conducted if there is no hope of affecting the state of the cancer. But clinical research can also be used to learn more about disease processes, the interactions between the rest of the patient's body and cancer, and the effects of therapy aside from anticancer activity. This is an area where several of the people with whom OTA spoke noted a lack of communication and coordination between basic and clinical researchers. If much more were known about the cancer process, and if treatment were at a more sophisticated stage, this might not be as important. As it stands, there is much that can be gained in the more basic research area through collaborative efforts with clinical researchers.

Centers Program

Since the early 1960's, NCI has conducted a Cancer Centers Program to provide grants for support of multidisciplinary programs in cancer research at educational and research institutions in the United States. Enactment of the National Cancer Act of 1971 marked the beginning of a period of rapid growth of the Cancer Centers Program. In addition to an increased number of centers, there has been a concomitant growth in their size and complexity, expansion of their research programs and activities, and augmentation of their professional staffs.

Cancer centers have developed in a number of different organizational settings: Some are independent, freestanding institutional entities; other are under the auspices of universities, often involving several colleges; and still others are consortia or multi-institutional in nature. Although a cancer center needs a certain minimum number of research programs for a "critical mass," existing centers vary greatly in size and breadth of programs—from rather small, specialized centers to large, complex comprehensive centers. They have developed from existing areas of strength at the parent institutions into coordinated multidisciplinary programs of several types (62):

1. Laboratory Cancer Research Centers (LCRC)—centers engaged *only* in laboratory research;
2. Clinical Cancer Research Centers (CCRC)—centers engaged *only* in clinical research; and
3. Cancer Research Centers (CRC)—centers engaged in *both* laboratory and clinical research.

In addition, a CRC with a funded Cancer Center Support Grant (CCSG) may apply to NCI for recognition as a Comprehensive Cancer Center. Such recognition may be granted by the Director of NCI if evaluation of the center demonstrates compliance with the guidelines for recognition of a cancer center as comprehensive. These guidelines were established by NCAB and were revised by the Board in 1979 (see addendum D). In fiscal year 1981, there were 20 Comprehensive Cancer Centers, 23 CCRCs, and 18 LCRCs (see table 19).

Cancer centers depend heavily on NCI for research and operational support funds. NCI contributes an average of 77 percent of total external support funds. Other NIH programs provide an additional 11 percent. The total NIH contribution is therefore 88 percent of all external financial support. The remaining 12 percent derives from other Federal, public, and private sources. Any changes in the NCI budget appropriation and its apportionment can be expected to have a significant impact on the centers' research and operational stability.

A number of areas of concern have been identified in the past regarding the centers program, directed mainly at the comprehensive centers and how well they carry out their role. From the beginning, the centers have been individualistic in organization and in their relation with the community. All were respected institutions in cancer research already, all with strengths and weaknesses in various areas. It is obviously advantageous for such institutions to be recognized by NCI, both financially and in terms of prestige, but the institutions did not rework themselves into a uniform mold, nor was that ever the intent of NCI. It does mean that criteria for naming and evaluating comprehensive cancer centers are fairly general, though specific requirements can be included.

Centers vary greatly in the degree of integration of basic and clinical research, though that link appears to be weak in some centers. The degree to which centers serve as focal points for the community or region also varies, but some are have a great deal of community involvement.

A longstanding criticism of the program is the lack of geographic coverage of the centers. One of the guidelines for comprehensive centers is "geographic impact." A comprehensive center "should increase the national capability to carry out regional trials, regional training, education and information dissemination activities." There are, however, two comprehensive centers each in Los Angeles and New York, and it appears that "scientific excellence" overrides concerns of geographic distribution. One NCI official ex-

Table 19.—Cancer Centers

Comprehensive cancer centers	Clinical cancer centers	Nonclinical cancer centers
Comprehensive Cancer Center University of Alabama at Birmingham	University of Arizona Cancer Center Tucson, Ariz	Stanford University Medical Center Stanford, Calif
Kenneth Norris, Jr., Cancer Research Institute University of Southern California Los Angeles, Calif	University of California at San Diego La Jolla, Calif	University of California Berkeley, Calif
UCLA Jonsson Comprehensive Cancer Center UCLA School of Medicine Los Angeles, Calif	Northern California Cancer Program Palo Alto, Calif	City of Hope National Medical Center Duarte, Calif
Colorado Regional Cancer Center, Inc.[a] Denver, Colo	Cancer Center of Hawaii University of Hawaii at Manoa Honolulu, Hawaii	Scripps Clinic and Research Foundation La Jolla, Calif
Yale University Comprehensive Cancer Center New Haven, Conn	Ephraim McDowell Community Cancer Network, Inc Lexington, Ky	Armand Hammer Center for Cancer Biology The Salk Institute La Jolla, Calif
Georgetown University/Howard University Comprehensive Cancer Center	Hubert G. Humphrey Cancer Research Center Boston University School of Medicine Boston, Mass	Purdue Cancer Center Purdue University West Lafayette, Ind
Vincent T. Lombardi Cancer Research Center Georgetown University Medical Center Washington, D.C.	Cancer Center, Tufts New England Medical Center Boston, Mass	Worcester Foundation for Experimental Biology, Inc. Shrewsbury, Mass
Howard University Cancer Research Center College of Medicine Washington, D.C.	Norris Cotton Cancer Center Dartmouth-Hitchcock Medical Center Hanover, NH	Center for Basic Cancer Research Washington University School of Medicine St. Louis, Mo
Comprehensive Cancer Center for the State of Florida University of Miami School of Medicine/ Jackson Memorial Medical Center Miami, Fla	Cancer Research and Treatment Center University of New Mexico Albuquerque, N.M.	St. Louis University St. Louis, Mo
Illinois Cancer Council		
Northwestern University Cancer Center Chicago, Ill	Cancer Research Center Albert Einstein College of Medicine Bronx, N.Y.	New York University Medical Center Institute of Environmental Medicine New York, N.Y.
University of Chicago Cancer Research Center Chicago, Ill		
Johns Hopkins Oncology Center Baltimore, Md	Hospital for Joint Diseases and Medical Center New York, N.Y.	American Health Foundation New York, N.Y.
Sidney Farber Cancer Institute Boston, Mass	Mount Sinai School of Medicine New York, N.Y.	Grace Cancer Drug Center Buffalo, N.Y.
Comprehensive Cancer Center of Metropolitan Detroit Detroit, Mich	New York University Medical Center New York, N.Y.	Case Western Reserve University Cleveland, Ohio
Mayo Comprehensive Cancer Center Rochester, Minn	University of Rochester Cancer Center Rochester, N.Y.	The Pennsylvania State University, College of Medicine Hershey, Pa
Sloan-Kettering Institute for Cancer Research/Memorial Sloan-Kettering Cancer Center	Cancer Research Center, University of North Carolina Chapel Hill, N.C.	The Wistar Institute of Anatomy and Biology Philadelphia, Pa
Roswell Park Memorial Institute Buffalo, N.Y.	Oncology Research Center Bowman Gray School of Medicine Winston-Salem, N.C.	Fels Research Institute Temple University Medical School Philadelphia, Pa
Columbia University, Cancer Research Center College of Physicians and Surgeons New York, N.Y.	Puerto Rico Cancer Center University of Puerto Rico, Medical Sciences Campus San Juan, P.R.	The University of Wisconsin, McArdle Laboratories Madison, Wis
Comprehensive Cancer Center Duke University Medical Center Durham, N.C.	Roger Williams General Hospital Providence, R.I.	
The Ohio State University Comprehensive Cancer Center Columbus, Ohio	Memphis Regional Cancer Center Memphis, Tenn	
University of Pennsylvania Comprehensive Cancer Center		
Institute for Cancer Research Fox Chase, Pa.	St. Jude Children's Research Hospital Memphis, Tenn	
University of Pennsylvania Cancer Center Philadelphia, Pa.	The University of Texas Medical Branch Hospitals Galveston, Tex.	
The University of Texas System Cancer Center M.D. Anderson Hospital and Tumor Institute Houston, Tex.	MCV/VCU Cancer Center, Medical College of Virginia Richmond, Va.	
Fred Hutchinson Cancer Research Center Seattle, Wash.	Vermont Regional Cancer Center, University of Vermont Burlington, Vt.	
The University of Wisconsin, Clinical Cancer Center Madison, Wis.	Milwaukee Children's Hospital Milwaukee, Wis.	

[a]Although this center does not have a current core grant, it is a recognized NCI Comprehensive Cancer Center.

SOURCE: National Cancer Institute, 1981.

plained that it was never the intent of the program to achieve geographic distribution of centers. It is understandable that there are no centers in areas where there are few large teaching or research medical institutions, but it appears that there is substantial overlap in populations served. The new CCOP program is intended to reach into the community with importance given to geographic spread, according an NCI official.

A number of experts contacted by OTA mentioned that the appearance of almost 2,800 oncologists and more than 3,000 oncology nurses in the past decade has been instrumental in improving care for cancer patients. Part of the expansion in the pool of well-qualified health professionals in this area is credited to the interest developed in cancer as a result of the National Cancer Program. In particular, the cancer centers are credited with having made major contributions to professional training.

> . . . even under the limited mandate of Cancer Control, providing for research and demonstration but not for health care, the program presents great opportunities for the NCPP [National Cancer Program Plan]. Thus, improvements in today's methods for the education and training of all the health professionals in the cancer fields, technicians, nurses, and physicians, would inevitably result in an upgrading of the quality of cancer care.
>
> If, as an early outcome of the NCPP, the country were to be provided with significant numbers of health professionals, trained in the use of specialized techniques and facilities, this would surely be recognized as a valuable product, solid and highly visible (44).

Centralized Cancer Patient Data System

The Centralized Cancer Patient Data System (CCPDS) began in 1977. The system is addressed at developing a uniform data system in the Comprehensive Cancer Centers. At this time all 20 Comprehensive Cancer Centers have been awarded grants to participate.

Under this system, 38 items of information are collected on each patient meeting certain criteria and reported to the Statistical Analysis and Quality Control (SAQC) center in Seattle, Wash. SAQC maintains the system, analyzes the data and acts as the coordinator for research activities involving CCPDS. Approximately 50,000 new cases are registered annually at SAQC (62).

Two basic goals of the system were to ensure that the comprehensive cancer centers used uniform language and procedures in naming and staging cancers and to develop a resource for cooperative research projects, drawing from all the centers. The first goal apparently has been achieved. Toward the second, a number of projects are in various stages of planning, using the system as a source of cases for case-control studies and studies of rare cancers.

The analyses produced by SAQC will deal mainly with survival of patients with various forms of cancer, representing those receiving the most sophisticated treatment in the country. The other major system for survival statistics, the SEER program (see above), differs in that it theoretically represents the survival of all cancer patients, including those treated in all types of facilities.

The question that arises is whether enough new information is gained from CCPDS to justify its existence. The improvements in statistical capability in the centers and the uniformity of language are undoubtedly of value. The aspects that might be seriously questioned are the emphasis on survival rates and the usefulness of a centralized system for carrying out research. NCI is conducting a concept review of CCPDS in the spring of 1982, to be carried out by an outside ad hoc committee. The committee will make recommendations for the future of the system at that time.

The Cancer Control Program

At the time of the passage of the National Cancer Act, "the scientific community and the Congress thought . . . that many research advances existed which could affect cancer, but these advances were not being disseminated and used. The cancer control program was intended to bridge this gap." (28).

The act directed that NCI was to establish programs with State and other health agencies

that were to demonstrate the best methods to apply the most recent advances in diagnosis, treatment, and prevention. The control program was not to perform research to develop new knowledge in those fields; rather it was to develop means for application.

In 1974 and 1978, the act was amended, and Congress mandated that NCI conduct cancer control programs aimed at diagnosing uterine cancer (by use of the "Pap" test). Other specific diagnostic programs—breast and oral examinations—were also mentioned in the legislative history that accompanied the act. NCI has since then carried out some demonstration projects dealing with these subjects. A massive Pap test demonstration was found to have missed its objectives and to have been poorly managed by NCI (28).

The cancer control program was administered from the NCI Director's Office until September 1974, when it was moved to the newly formed Division of Cancer Control and Rehabilitation. In 1980, an NCI reorganization formed the Division of Resources, Centers, and Community Activities (DRCCA), and cancer control was placed within it. This recent organization brought to the division all NCI programs connected with control and technology transfer. From 1976 through 1980, $302 million were allocated to the cancer control program as a line item in the NCI budget. More than two-thirds of that amount has been obligated for contracts.

GAO Review of the Program

A GAO audit (28) of three completed cancer control contracts found that many specified tasks were never accomplished. GAO found, to some extent, that a shortage of NCI staff had contributed to poor contract supervision and the subsequent failure of the contracts to reach their goals. Beyond the staff shortage, GAO found that poor cooperation among NCI staff and poor management contributed to the failures of the contracts.

Two contracts reviewed by GAO were to provide assistance to populations of workers who had been expected to develop a large number of tumors because of workplace exposures. In both those cases, so few tumors developed that there was no point to the demonstrations. It might be that more attention to the planning of those studies would have revealed the likelihood of there being too few tumors, and the expense of setting up the demonstrations could have been avoided.

The GAO audit (28) interviewed a number of "NCI officials and current and past advisors to the control program . . . . the individuals said this assumption [that medical advances in cancer were slow to get into practice] proved to be incorrect because few cancer advances existed that the medical community was not using." Despite that conclusion, four out of five advisors expressed opinions that the program in some form ought to be continued.

An NCI official, interviewed by OTA as part of this study, said that the cancer control programs in the 1970's had not been very good. They were, he said, motivated by a desire to do good things in the community. However, they lacked detailed planning, reachable objectives, and evaluation. The official is confident that recent initiatives (such as the Community Clinical Oncology Program (CCOP), see below) will improve the performance of the cancer control activities.

A Critical View of the Cancer Control Program in Contrast to the Success of Cancer Control

The value of NCI programs in cancer control projects is dismissed in an article by Yarbro that points to major improvements in the treatment of cancer in the community (119).

> Let's go back to square one for a moment . . . to what everyone already knows. Research is finding out which treatment is best: Control is making that treatment available. Now, I submit that we and the NCI know a great deal about cancer research, but precious little about cancer control. . . . Why?
>
> To explore the answer to that question, let me present you with a paradox: The Cancer Control Program of the NCI has been a dismal failure, and yet, the quality of cancer care at the community level has improved in quantum leaps every year. How can a program so gener-

> ally agreed to be such a disaster have succeeded so magnificently? The answer, of course, is that what we *defined* and *funded* as cancer control had nothing at all to do with the remarkable progress in cancer care at the community level.

Yarbro goes on to say that great improvements in the community have occurred in facilities, personnel, and treatment protocols (119). He says that better facilities have come from "hospitals and doctors . . . competing with each other to provide the best." This was "competitive cancer control," he says, neither planned nor NCI-funded.

According to Yarbro, "We now have more than enough oncologists in practice and in the pipeline to serve cancer patients for years to come." NCI training programs have contributed to this supply, but they are fading because of funding cutbacks. However, the university need for trainees ("the ones to do all the work") ensures the continued production of trained personnel. Finally, Yarbro concludes (119):

> So much for facilities and personnel. What about new treatment protocols? Surely we need special people (at Federal expense) to carry these from the university centers to community hospitals! Here I am forced to admit that the Federal government has been heavily involved. It *does* pay such people. They are called postmen and they deliver medical journals. With few exceptions, new treatment protocols enter community use when oncologists read journals or attend meetings. This is *self-education* cancer control!

Yarbro is positive about enlisting community physicians in clinical trial programs. It will, he says, facilitate movement of new therapies to the community which will benefit patients. At the same time, it will "unleash the awesome power of the private practice sector in clinical research."

In addition to the involvement of community physicians in clinical trials, Yarbro sees a need for some demonstration projects. The widespread distribution of "hospital cancer programs with (tumor) registries, tumor boards, and guidelines" should be a goal for the 1980's. He sees demonstrations of workable methods to reach that goal as worthwhile projects for cancer control.

Yarbro's opinions represent an extreme, but they illustrate questioning of the basic tenet of the cancer control program. Is there a lag in transfer of research information to the community setting? Any answer to that question is likely to be qualified. GAO interviews with NCI officials and advisors were almost consistent in saying that cancer control programs may have accelerated the transfer, but that transfer would have occurred, perhaps more slowly, in their absence (28).

Opposing Views About Technology Transfer

Sharply differing opinions about cancer control were voiced during hearings of the Investigations and General Oversight Subcommittee of the Senate Committee on Labor and Human Resources on May 21, 1981 (9). Some witnesses said that publication of research findings does not constitute effective communication of information and that NCI needed to develop better means for technology transfer.

Also discussed at those hearings was the role of clinical trials in technology transfer (9). Methodist Hospital, Indianapolis, Ind., therapist William Dugan said that it would be "inappropriate to substitute clinical trials for cancer control."

An opposing view was expressed by Harold Amos, a member of the President's Cancer Panel and NCAB (9). Amos said, "Clinical trials are technology transfer." The establishment of research advances "as clinical practice throughout the land, admittedly of utmost importance, must be the task of some other network already in place." Amos viewed suggestions for increased emphasis on technology transfer "as a threat to divert NCI from the one thing it was created to do and can do admirably, i.e., conduct and develop programs in research into the etiology, diagnosis, prevention, and treatment of cancer. In that role its resources are already overtaxed."

These differences illustrate the varied positions taken on the subject of technology transfer. There is no doubt that research advances

need to be applied, but there is disagreement about whether or not special methods are necessary to transfer those advances. Beyond that, if methods are needed, there is another question about whether NCI or some other organization is appropriate to manage the transfer.

Goals of the NCI Cancer Control Program

In 1979, NCI described the cancer control program as focused on (28):

- identifying, evaluating, and planning the application of innovative, practical methods of cancer control;
- developing demonstration programs to promote the use of effective cancer control methods by the Nation's health professionals;
- developing training resources for educating health professionals in the use of cancer control interventions;
- developing methods of encouraging beneficial attitudes and lifestyles as they relate to the control of cancer with emphasis on hard-to-reach populations, such as minority groups and blue collar workers;
- providing mechanisms for organizing the Nation's resources for an effective, coordinated attack on specific cancer control problems.

Early in 1982, major attention had been focused on CCOP that will involve community physicians in trials of new treatment protocols. This program, described below, is an example of attention to the second goal in the list above.

NCI is also planning to emphasize education about workplace exposures that have been associated with cancer. In the past few years, NCI has had an interagency agreement with the Occupational Safety and Health Administration (OSHA) for its New Directions Program. That program funded cancer-related educational efforts by employers, employees, unions, and academic institutions to improve workplace health and safety. During 1981, OSHA eliminated its peer review of New Directions grants, and NCI has decided to fund a limited, similar program. It is now considering different methods to reach the groups described in the fourth goal above.

Community Outreach and Rehabilitation Branch Activities

The Community Outreach and Rehabilitation Branch supports programs designed to (62):

- increase the transfer of cancer management technology from research centers to the community;
- develop effective cancer management capabilities within the community;
- continue the development of rehabilitation devices and strategies;
- develop new approaches to the management of pain associated with cancer; and
- study the problem of optimal care for the terminally ill cancer patient.

The Community Outreach and Rehabilitation Branch supports the following programs, which are described in the sections below (62):

1. Clinical Cooperative Group Programs.
2. Clinical Oncology Programs.
3. Community Hospital Oncology Programs.
4. Community Clinical Oncology Programs.
5. Rehabilitation Program.
6. Pain Programs.
7. Hospice Program.

Clinical Cooperative Group Programs

According to NCI (62):

> The reduction of cancer morbidity and mortality in the community setting is the goal of the Cooperative Group Outreach Programs. The objectives of these programs are to upgrade the skills of community physicians and other health professionals in the management of cancer patients and to increase the number of these patients receiving the best available care.
>
> The objectives are being fulfilled by the mechanisms of increasing the number of community hospitals affiliated with the cooperative groups, expanding the groups' referral networks, providing support services to the community hospitals, and developing a broad range of profes-

sional educational programs at both national and regional meetings and workshops.

The involvement of community hospitals with these groups, originally comprised of university hospitals and other major cancer centers, is a recent phenomenon (see Eastern Cooperative Oncology Group Community Hospital Program, below). In 1980, six cooperative groups had outreach activities supported by either a grant or contract.

ECOG Community Hospital Program.—The Eastern Cooperative Oncology Group (ECOG) Community Hospital Program is discussed as a specific example of technology transfer activities. In the early 1970's, in large part as a result of the success of NCI-funded training programs, a growing number of cancer patients were being treated by trained oncologists in community hospitals, as opposed to being treated in major teaching or research hospitals. Recognizing this trend and the importance of involving community hospitals in the cancer control effort, one of the NCI-funded Cooperative Groups, ECOG, applied for funds to be used for supporting the participation of community hospitals in clinical trials. The application was rejected on grounds that community hospitals should not be participating in clinical trial research. However, the next year NCI initiated a program to allow for just such involvement of community hospitals, and in October 1976, NCI awarded funds to ECOG to begin the ECOG Community Hospital Programs.

The first 5 years of the ECOG Community Hospital Program have been a great success in the participation of community hospitals and in the quality of data they have submitted (5). At present, 112 community hospitals are participating, having enrolled in protocol studies over 5,000 patients in 5 years, now averaging well over 1,200 patients per year. Perhaps more important, the quality of participation in ECOG clinical trials and the patient outcomes in community hospitals were no different than those for member institutions. The success of the ECOC program has been one factor in encouraging NCI to embark on CCOP.

An individual associated with ECOG expressed great dissatisfaction with NCI involvement in the Community Hospital Program. There was resistance to the program at a time when it was obvious to the ECOG people that the community should have been involved. There seems to be little doubt that ECOG has taken a successful approach to involving community hospitals in clinical trials (6), and the approach has also worked for some other cooperative groups. NCI is planning to make a very large investment in CCOP, a program that many see as competing with the ECOG type programs, and which will be organized in a manner quite opposite to them. In CCOP, the community hospitals (or consortia) will apply directly to NCI, and it will be each hospital's (or consortia's) responsibility to find a research base with which to affiliate. Financial incentives and autonomy for the community hospitals may be greater in CCOP than through the cooperative groups, and the possibility exists that the cooperative groups may be irreparably damaged. The request for applications (RFA) for CCOP has not yet been released, and the criteria for awards are not yet fully known, so these potential problems may be ironed out before the program gets underway.

Clinical Oncology Programs

Community hospitals or consortia of hospitals were funded under the Clinical Oncology Program (COP) to demonstrate that effective multidisciplinary diagnosis, treatment and rehabilitation services can be provided to patients in community setting, through small cost-sharing contracts. Criteria against which community participation are measured are (62):

- involvement of physicians, nurses, and other allied health professionals in initial planning of a community treatment and referral system for the patient;
- participation of physicians and allied health professions in designing multidisciplinary guidelines for patient treatment, nursing care, rehabilitation and terminal care;
- funding and direction of the cancer programs by a locally accepted hospital or fiscal agent of the regional consortia;

- practical relationships concerning patient treatment that can be developed with regionally appropriate universities or comprehensive cancer centers; and
- leadership, in the form of an individual or group that can motivate a community to cooperate for the benefit of the cancer patient and family.

Five COPs have completed 3 years of implementation. The final contract year has been devoted to evaluation with support for operational aspects of the program assumed by the community. Analysts of the experiences of the pilot COPs resulted in a model approach to the development of Community Hospital Oncology Programs (CHOPS).

Community Hospital Oncology Programs

According to NCI (62):

> Twenty-three contracts have been awarded to field test (in single institutions, community consortia of institutions, and rural institutions) a model approach to development of a community cancer program.
>
> The purpose of these CHOPS is to provide evidence that implementation of the COP model in a community will improve the scope and quality of cancer care for cancer patients over that received prior to development of the program.
>
> In the development and implementation of each program, the cooperating hospitals and health care professionals will:
>
> - define criteria for cancer patient care through the development of management guidelines;
> - plan and implement a program to encourage community cancer care practices in accordance with these criteria for care;
> - use a data management system (e.g., through upgraded tumor registries) to assess the extent to which community cancer care practices correspond to the recommended criteria; and
> - use the information obtained to correct, modify, and improve the clinical oncology program and to document effective changes in community cancer care.
>
> The 23 CHOP contractors are in an 18-month planning phase. Contractors submitting satisfactory implementation plans will be eligible for a further two-year implementation contract.

Implementation and evaluation plans resulting from the first 12 months planning activities have been submitted as proposals for peer review.

Community Clinical Oncology Program

The NCI Director has put a high priority on funding CCOP, a new program designed to involve small community hospitals and community oncologists in NCI-sponsored clinical trials. NCI will provide resources for the hospitals to join forces with large institutions already involved in NCI-supported research. Through this arrangement, a technology flow from NCI to the community will be established.

The impetus to initiate CCOP came, in part, from a directive of Senator Hawkins asking NCI to upgrade the quality of cancer treatment in community hospitals. The program was "concept-approved" in the fall 1981 and an RFA was prepared. The RFA was scheduled for release in April 1982, but NCAB at its February 1982 meeting expressed interest in knowing the contents of the RFA before release. An NCAB subcommittee reviewed a letter from NCI that describes the contents of the RFA in early March 1982. The subcommittee has decided to review the CCOP concept and plan and report to the full NCAB in May.

Up to 200 CCOP units are expected to be funded initially. Estimates of the number of applications expected range from 100 to 1,000. Geographical distribution will be considered among other factors in making decisions about where to fund units.

Rehabilitation Program

According to NCI (62):

> This program seeks to reduce the morbidity from cancer and its treatment through stimulating study, demonstration, and research in new techniques of rehabilitation that have specific applicability to the physical, cosmetic, and functional problems associated with cancer.
>
> The comprehensive nature of cancer rehabilitation determines support for a variety of projects that seeks to achieve the cancer patients' early adjustment and re-entry into the everyday

world of work, social activity, and physical functioning.

The rehabilitation program supports 21 grants which presently investigate six major areas of cancer rehabilitation, and four contracts to support training for dental personnel interested in pursuing postsurgical restorations for cancer patients.

Pain Programs

NCI states (62):

> Pain is one of the most feared consequences of cancer. Severe pain generally occurs in advancing and terminal disease, and pain may also be an early manifestation of cancer or its presenting symptoms. Cancer pain has been the focus of considerable attention and concern for clinicians, patients, their friends and families, the general public, and the Government. However, it is now the consensus that no adequate data base exists from which to determine the true magnitude of the cancer pain problem. DRCCA has initiated pilot studies of cancer pain with the goal of gathering valid data defining the incidence and natural history of pain in cancer. Under the contract program *Pain Control in Cancer*, seven institutions are participating in a collaborative study to demonstrate that pain control for cancer patients is best instituted early in its onset after careful planning and evaluation by a multidisciplinary team of experts. This program addresses the management of pain associated with advanced and metastatic diseases and chronic pain associated with localized disease.

Hospice Program

According to NCI (62):

> Three projects in *Implementation of the Hospice Concept for the Care of Terminal Cancer Patients* were implemented with a home care program and a backup in-house facility. These projects provided a demonstration of comprehensive terminal care given in three different settings, i.e., a nursing home, a community hospital, and a health maintenance organization. A collaborative, descriptive study developed by the hospice contractors and NCI program staff was implemented in October 1979 with data collection ending September 30, 1980. The study focused on a thorough description of care in the three settings which included a longitudinal assessment of the patient and the bereaved family members (significant others). In describing the hospice patient population, age, sex, socioeconomic status, medical condition, and other pertinent characteristics were recorded. Data analysis is proceeding and a report is to be available by the end of this year.

PREVENTION PROGRAMS

The goals of the NCI cancer control program include "developing methods of encouraging beneficial attitudes and life styles . . ." A number of experts with whom OTA talked mentioned two areas that may deserve special attention because of their importance to prevention programs. Those two areas, epidemiology and nutrition research, are discussed below.

Epidemiology

In 1975, the Environmental Epidemiology Branch was created in the Division of Cancer Cause and Prevention, and has expanded in size and budget. The objective of the branch has been to attain a comprehensive and balanced program to enhance our capacity at the national level to generate fresh ideas and help settle key questions in cancer epidemiology and etiology. Along with expansion of the intramural and collaborative programs, parallel efforts were made to stimulate and encourage extramural grant-supported programs in epidemiology, including some support for training in epidemiology and biostatistics.

The epidemiology and biometry program of NCI plays a pivotal role in the National Cancer Program. It has responded to requests at all levels to increase the scope of its work and to help develop Federal programs and policies in several areas. NCI efforts have contributed not only to research in cancer etiology, but also to our understanding of natural history, end results, clinical trials, preventive measures, and strategies involved in administrative planning

and decisionmaking. Increasingly, epidemiologic and biometric approaches permeate various aspects of the National Center Program, and are fundamental to the design and evaluation of methods to control cancer."

In spite of the laudable achievements of the last few years, a number of people that spoke with OTA expressed strong feelings that NCI has failed to emphasize epidemiology sufficiently.

Much of the information available today about how to prevent cancer has come from epidemiology. The convincing evidence that cigarettes, asbestos, radiation, and some chemicals definitely cause cancer is based on epidemiologic studies. There is a lack of consensus about whether or not there are many good epidemiologic hypotheses that are going untested because of lack of support for training in epidemiology and biostatistics. Support for such training is seen as always having been minimal, and as being further reduced in recent budget tightening. The lack of trained people in this area has been recognized for many years and has been publicized by the National Research Council.

Primary prevention—preventing cancers from developing at all—is the ultimate goal, and it depends to a large extent on epidemiology. That is not, however, a practical short-term goal or even a foreseeable goal. Epidemiology, however, is a necessary component of other aspects of cancer control. For example, screening programs, leading to early diagnosis of existing cancers, have been a major thrust of secondary prevention efforts at NCI. Yet, some screening programs have been misapplied. One of the experts who spoke with OTA claimed that as much was known about the Pap smear as a successful technique for detecting cervical cancer in 1941 as is known today. In the 1960's, as part of the cancer control program, a demonstration screening program was initiated, but it was directed at a segment of the population that would benefit little from it. Some experts contend that the same thing is happening today in breast cancer screening. Increased epidemiologic input would reduce the chances of such misapplications. Epidemiologic guidance could be the integrating factor between the clinic and the community, identifying the population groups who would derive the greatest benefit from screening.

Epidemiology might be a unifying force between different phases of research, but in the past, resources for epidemiology have been relatively small compared to other parts of NCI. There are hopeful signs at present of expansion in epidemiologic efforts.

Nutrition Research

Components of diet are associated with cancer occurrence. During Senate hearings in 1978, a large number of witnesses referred to estimates that 60 percent of cancer in females and 40 percent in males were related to diet (115). Relationships are not always clear, but some associations between dietary components and cancer *risks* are widely accepted. For instance, high-fat diets are associated with elevated colon and breast-cancer rates. Such findings produce immediate suggestions for reducing cancer incidence. The Division of Cancer Cause and Prevention has been active in looking at dietary risk factors for cancer in a number of epidemiologic studies.

Within the last year, a number of studies have contributed to the hypothesis that eating beta-carotene, a precursor of vitamin A found in green, leafy plants and carrots *reduces* cancer incidence (20,86,96,106). Identification of protective components in the diet may be as important for prevention as is describing risk factors.

Nutrition has also been studied in relation to cancer treatment. Many cancer patients have no appetite and have difficulty in "keeping food down;" they waste away during treatment. The term used for providing nutritional support to the patient is "hyperalimentation." Although the Senate heard some presentations about nutritional support of the patient, it is clear from the hearing record that Congress was most interested in cause and prevention.

Another example of interest in nutrition and cancer is a major National Academy of Sciences' study of that subject that is now underway. Its report is expected in late 1982.

J. F. Fraumeni, Jr., NCI, personal communication, Mar. 10 1982.

At least partly as a result of congressional interest in the nutrition-cancer link, NCI established a program in this area. Many early efforts of the program were directed at treatment, not at cause and prevention. Presentations from that program that are described in the NCAB annual reports in the late 1970's discussed hyperalimentation.

A change in direction is now apparent. NCAB's Subcommittee on Nutrition and Cancer has recently examined NCI's efforts in this field, and it has recommended a time-limited allocation of funds to stimulate cancer-nutrition research and the establishment of a task force to coordinate NCI efforts (71).

"Chemoprevention" has become a popular word in the cancer lexicon. It refers to identification of agents that can be ingested with the expectation of reducing cancer. The NCAB subcommittee published a list of the 10 chemoprevention trials that are ongoing at NCI. Eight of the 10 trials are being conducted in cancer patients, and, therefore are aimed at prevention of recurrent or worsening disease. Only one study of the 10 is directed at primary prevention in general populations. It is a study to be conducted in a population of 21,900 healthy males, ages 50 to 75. The study is designed to test the effectiveness of beta-carotene in reducing cancer occurrence and to test the effectiveness of aspirin in reducing heart attacks. This large-scale study is being jointly supported by NCI and NHLBI. The contrast between this chemoprevention study, involving a large number of healthy people and prevention strategies directed at the number one and two killers, and the other chemoprevention trials needs no elaboration.

A number of experts who were contacted by OTA make a point of the difficulties of executing these studies. Such studies involve a large number of people in making changes, albeit small ones, in their lifestyles, and the studies will be difficult. Though it is a first step, merely carrying out such a study is no guarantee that meaningful results will be obtained.

The NCAB subcommittee, which was critical of the current efforts in nutrition research, draws attention to the possible lack of good, testable ideas in nutrition and cancer, and proposes a number of changes at NCI to promote better research in this area. Such changes may lead to better understanding of the connections between diet and cancer.

SUMMARY

Improvements have been made in the control of cancer. The reasons for some of the improvements are well understood. The reasons for some others remain obscure.

Some encouraging changes in incidence and mortality are apparent. Lung cancer mortality has decreased as a consequence of changes in smoking patterns in young males. Decreased stomach and uterine cancer incidence have resulted in declines in mortality. Improved treatment regimens have dramatically reduced mortality from some cancers.

NCI research has played a major role in these improvements. The role of formal cancer control programs and technology transfer activities in moving improvements to the community is less clear. Management of technology transfer is a difficult task, and NCI is trying a number of activities to decide upon effective strategies. A related, also difficult task, is the development of measures for the success or lack of success of technology transfer programs. A new focus of cancer control at NCI will be the Community Clinical Oncology Program (CCOP), which, like the successful Clinical Cooperative Oncology Group (CCOG) Program, will involve community physicians in NCI-sponsored clinical trials. These programs directly transfer the most recent treatment and management methods to the community through physician participation. Experts contacted by OTA were complimentary about NCI's role in the progress being made against cancer and in understanding the disease; at the same time, some expressed concerns about some features of its many programs. Those concerns are not definitive opinions, but they identify difficult issues that merit attention.

ADDENDUM A: GROWTH OF THE NATIONAL CANCER INSTITUTE AFTER PASSAGE OF THE NATIONAL CANCER ACT

The NCI Budget

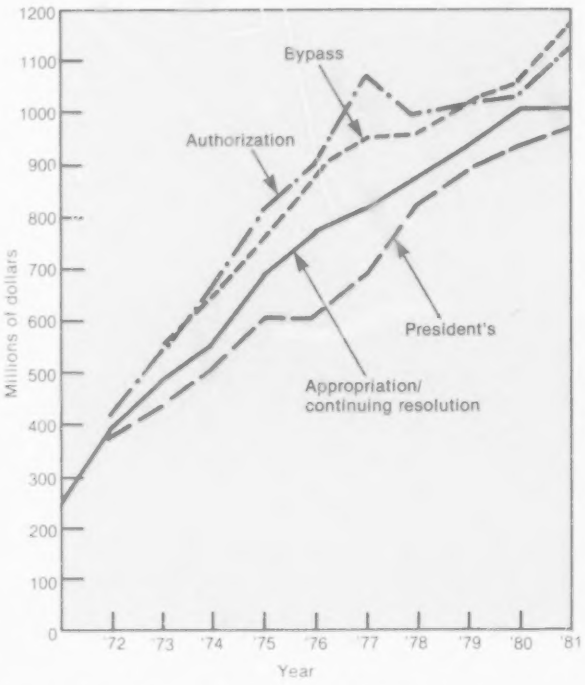
Financial support for NCI more than doubled between 1972 and 1981 (see table 20 and fig. 4). The budget includes funds for both cancer research and cancer control; the dollar amounts in this section are the sums for both activities.

The NCI budget exists in four forms. The annual authorization figure is the amount specified in the enabling legislation. It and the "bypass request," which is a budget prepared by NCI staff and advisors, have been for approximately the same amounts each year and have increased almost in parallel since 1972. By legislative authority, the bypass request is submitted directly to the President and bypasses the budget process imposed on other components of the Public Health Service (PHS) and the Department of Health and Human Services (DHHS) by the executive branch. The Department may comment on the bypass budget but cannot change it.

The "President budget request" is the final amount proposed by the administration after the President and the Office of Management and Budget have reviewed and evaluated the bypass request. That mark has been consistently below the bypass request, and during 1973 through 1977, it ran between 64 and 82 percent of the authorization (see table 21 and fig. 5). However, because the percentage increase in the President's request in recent years has been greater than the increase in the authorization, the President's budget has been 85 percent or more of the authorized figure for the last 3 years.

The final budget figure, the continuing resolution or appropriation figure, is the amount of money

Figure 4.—Authorized, Requested, and Appropriated Budgets of NCI, Fiscal Years 1972-81



SOURCE: Office of Technology Assessment from NCI data.

Table 20.—Authorized, Requested, and Appropriated Budgets of NCI, Fiscal Years 1972-81

	Authorization[a]	Bypass request	President's budget request	Continuing resolution/ appropriation
1972	$ 420,000,000	—	$374,338 000	$ 378,794,000
1973	530,000,000	$ 550,790,000	432,205,000	492,205,000
1974	640,000,000	640,000,000	500,000,000	551,191,000
1975	803,500,000	750,000,000	600,000,000	691,666,000
1976	898,500,000	898,500,000	605,000,000	761,727,000
1977	1,073,500,000	948,000,000	627,670,000	815,000,000
1978	1,008,150,000	955,000,000	818,936,000	872,388,000
1979	1,015,000,000	1,036,000,000	878,802,000	937,129,000
1980	1,030,000,000	1,055,000,000	936,958,000	1,000,000,000
1981	1,128,600,000	1,170,000,000	965,105,000	1,001,330,000

[a]Includes both cancer control authorization and research authorization.

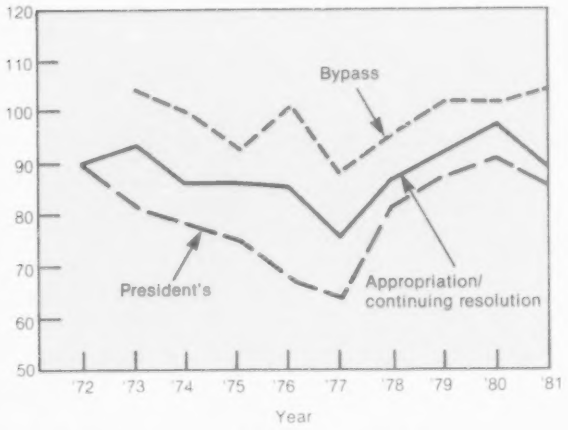
SOURCE: National Cancer Institute, Jan. 4, 1982.

Table 21.—Requested and Appropriated Budgets of NCI, as Percentages of the Authorized Budget, Fiscal Years 1972-81

	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981
Bypass	—	104%	100%	93%	100%	88%	95%	102%	102%	104%
President's budget	89%	82	78	75	67	64	81	87	91	85
Appropriation	90	93	86	86	85	76	86	92	97	89

SOURCE: Office of Technology Assessment from data in table 20.

Figure 5.—Requested and Appropriated Budgets of NCI, as Percentages of the Authorized Budget, Fiscal Years 1972-81



SOURCE: Office of Technology Assessment from NCI data.

Table 22.—Annual Percentage Increase in the NCI Appropriation Compared to Increase in the Consumer Price Index, 1972-81

	(1)Percent change in NCI appropriation over previous year[a]	(2)Percent change in Consumer Price Index[b]	(3)Net change in NCI budget (1) -(2)
1973	13.9	6.2	7.7
1974	34.8	11.0	23.8
1975	20.3	9.1	11.2
1976	8.8	5.8	3.0
1977	7.1	6.5	0.6
1978	7.2	7.6	(0.4)
1979	7.4	11.5	(4.1)
1980	6.5	13.5	(7.0)
1981	0.1[c]	13.5[d]	(13.5)

Increase in purchasing power of NCI between 1972 and 1981 after adjusting for inflation:

1972 dollar = 0.798 purchasing power of 1967 dollar[e]
1981 dollar = 0.397 purchasing power of 1967 dollar
1981 dollar = $\frac{0.397}{0.798}$ 1972 dollar = 0.498

1981 appropriation = $1,001 million × 0.498 = $498 million in 1972 dollars.

Therefore, actual increase = $498 million (1981 appropriation in 1972 dollars) - $379 million (1972 appropriation) = $119 million increase over period 1972-1981 = $119/379 million = 31 percent.

[a]1980 NCI Fact Book.
[b]Consumer Price Index for urban wage earners and clerical workers, table 22, *Statistical Abstracts of the United States*, 1981.
[c]Calculated from data in table 20.
[d]Rate for 1981 is based on the annual rate calculated from changes between Jan. and May in table 23, *Statistical Abstracts of the United States*, 1981.
[e]Calculated is reciprocal of "all items" Consumer Price Index in *Statistical Abstracts of the United States*, 1981.

SOURCE: Office of Technology Assessment.

received by NCI each year. Despite the fact that in some years either the President's request or the appropriation figure showed little or no increase, the sum of money received by NCI has increased each year except in 1981. The overall impression is that, until 1981, an increase in either the bypass request or the President's request signaled an increased appropriation. In 1981, there was hardly any appropriation increase, even though the authorization, the bypass request, and the President's request increased.

Appropriations increased most rapidly during the period 1972 through 1976, the first years of the National Cancer Program. In fact, had the NCI budget continued to increase at that rate, appropriations would have doubled every 3½ years. The rate of increase dropped significantly between 1976 and 1980 however, so that the period of very rapid growth in NCI appropriations occurred over only a few years.

Increases in NCI's appropriations exceeded the inflation rate for the period 1972 through 1977 but not since then (see table 22). The impact of inflation has reduced the purchasing power of the 1981 NCI appropriation to $498 million in 1972 dollars. In other words, after allowing for inflation, the NCI appropriation increased only about 31 percent between 1972 and 1981.

Research costs are a small part of the national expenditure on cancer. The National Center for Health Statistics estimates that cancer accounts for 10 percent of the cost of illness in 1977. Assuming that percentage remained constant, $24.7 billion was spent on cancer in 1980. During that year, the NCI

budget was $1 billion or less than 5 percent of the total cost of the disease.

Research Support From NCI Since Passage of the National Cancer Act

The NCI research budget can be divided between intramural projects and extramural projects (see addendum B). In 1980, about 17 percent of NCI's expenditures were for intramural research. The amount spent was $197 million as compared to $802 million spent extramurally in grants and contracts (see addendum B).

The number of extramural grant applications submitted to NCI, the number of applications approved for funding, and the number funded are shown in table 23 and figure 6. "Competing" applications (see table 23) are those for which no NCI money has been awarded for the period for which funds are being requested. They can be either of two types. "New" competing applications describe a project that is not currently being supported by NCI. In general, grant applications usually request funds for 3 to 5 years, and, if an award is made, the award is usually for 3 years. "Renewal" competing applications describe continuations of currently supported research, but the current grant period will expire at the time for which continuing support is sought. For instance, suppose that Investigator A had submitted a new competing application in 1977 that was successful and that a 3-year award was made to begin on January 1, 1978. If the scientist wished to continue that line of research, sometime late in 1979 or early 1980, he or she would submit another application. That application, coming from a supported investigator, would be a "renewal."

During the period of Investigator A's first grant, he or she would receive two "noncompeting" (see table 23) awards, in 1979 and 1980. This bookkeeping results from grants being made for more than 1-year periods but dollar allocations having to be made on a yearly basis.

Competing applications must cross the peer review hurdle to obtain funding. In this process, they are either "approved" or "disapproved." Approval means that the research outlined in the application is worthy of support. Each approved application is then awarded a numerical score. In general, applications with the best scores are funded.

Renewal applications fare significantly better than do new ones. The approval rate is higher and the percentage of approval applications funded is also higher (table 23 and fig. 6). The better performance of renewals is to be expected.

The number of awarded grants (both competing and noncompeting) increased from 1,834 to 2,555 between 1974 and 1980 (table 23 and fig. 6). The bulk of that increase, from 2,113 to 2,555, came during the years 1978, 1979, and 1980. Therefore, that increase occurred after the days of halcyon budget increases between 1974 and 1977 (see above). The increased number of regular research grant awards represents a reprograming of funds at NCI and increased emphasis on investigator-initiated grants. The percentage of NCI's extramural support going to investigator-initiated research grants increased from 52 percent (1974) to 66 percent (1980). The average value of grant awards has almost doubled during the 7 years 1974 to 1980 (table 23).

In 1974, 18.5 percent of NCI's extramural expenditures was for research support contracts and interagency agreements. During the next 4 years, the percentage varied between 17 and 19 percent, and in 1979 and 1980 it increased to 21.9 and then 23.6 percent (62).

NCI Support of Basic Research

NCI expends a smaller proportion of its resources on basic research than does the rest of NIH as a whole (see table 24). Its expenditure of 33 percent of its funds is also the smallest percentage spent on basic research by any institute. The National Institute of Dental Research (NIDR) spends the next lowest proportion for basic research, 44 percent. The National Institute of General Medical Sciences (NIGMS) spends the greatest proportion, 74 percent.

NCI spends 28 percent of all research and development funds spent by NIH. It spends 18 percent of the basic research dollars; and 35 and 57 percent, respectively, of applied research and development funds (table 24).

Because of NCI's spending distribution, it spends a larger percentage for "applied research" and "development" than the rest of NIH as a whole (table 24). Despite NCI's spending a low proportion of its funds on basic research, it spends more than any other institute because of its large budget ($382 million from a budget of $958 million); NHLBI spends the next largest amount ($302 million from a budget of $530 million) on basic research.

Among the many forces that play on NCI are ones that urge greater support of basic research. Other opposing forces want greater support for applied research and development. In OTA's conversations with experts about NCI, one end of a spectrum was represented by those who strongly favored investigator-initiated research programs, grant support, and limited centralized planning. At the other end were

Table 23.—NCI Regular Grant Awards—1974-80 (including clinical cooperative groups)
(dollars in thousands)

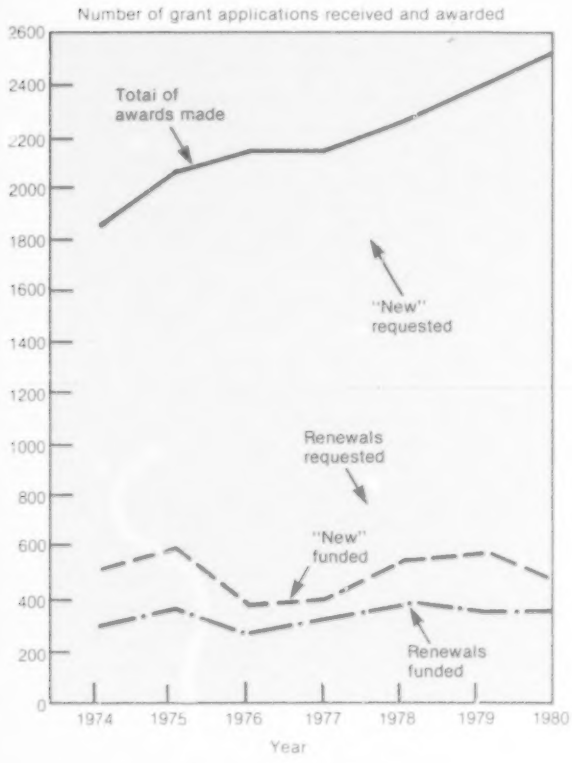
Type award	Requested		Approved		Awarded		Percent funded
	Number	Amount	Number	Amount	Number	Amount	
1974							
Competing							
New	1,382	$100,717	909	$ 45,713	500	$ 27,824	55.0%
Renewals	379	33,651	336	22,815	285	20,413	84.8
Total	1,761	134,368	1,245	68,528	785	48,237	63.1
Noncompeting	—	—	—	—	1,049	62,803	—
					Average	$ 34,200	
1975							
Competing							
New	1,509	$108,621	979	$ 48,023	581	$ 30,605	59.3
Renewals	555	55,314	429	31,876	349	27,949	81.4
Total	2,064	163,935	1,408	79,899	930	58,554	66.1
Noncompeting	—	—	—	—	1,112	72,917	—
					Average	$ 35,700	
1976							
Competing							
New	1,499	$113,135	910	$ 47,342	388	$ 22,230	42.6
Renewals	517	53,992	376	28,070	257	21,236	68.4
Total	2,016	167,127	1,286	75,412	645	43,466	50.2
Noncompeting	—	—	—	—	1,486	108,818	—
					Average	$ 51,100	
1977							
Competing							
New	1,756	$147,591	1,071	$60,155	398	$ 23,781	37.2
Renewals	728	87,162	578	50,221	303	32,436	52.4
Total	2,484	234,753	1,649	110,376	701	56,217	42.5
Noncompeting	—	—	—	—	1,412	104,431	—
					Average	$ 49,400	
1978							
Competing							
New	1,854	$153,528	1,264	$ 75,014	513	$32,591	40.6
Renewals	752	97,937	617	57,131	381	38,905	61.8
Totals	2,606	251,465	1,881	132,145	894	71,496	47.5
Noncompeting	—	—	—	—	1,341	111,916	—
					Average	$ 50,100	
1979							
Competing							
New	1,950	$177,989	1,414	$ 97,596	576	$ 45,287	40.7
Renewals	653	80,521	570	52,012	334	35,025	58.6
Total	2,603	258,510	1,984	149,608	910	80,312	45.9
Noncompeting	—	—	—	—	1,485	141,198	—
					Average	$ 60,300	
1980							
Competing							
New	1,891	$188,988	1,401	$103,389	470	$ 37,605	33.5
Renewals	632	89,866	610	62,289	346	39,167	56.7
Total	2,523	278,854	2,011	165,678	816	76,772	40.6
Noncompeting	—	—	—	—	1,739	171,312	—
					Average	$ 67,000	

NOTE: *Average* dollars presented in this column represent the total amount of money expended on grants divided by the number of grants. That dollar value is expressed in dollars, *not* in "dollars in thousands."

SOURCE: National Cancer Institute, 1981.

those who, while acknowledging the importance of basic research, favored more emphasis on centralized planning and grant and contract support of opportunities for making improvements in treatment. To a major extent, people in the first group view most of cancer problems as being in the "prefeasible" stage. They see an absence of understanding of cancer that can be overcome only by basic research. The second group see many more cancer problems as being in the "feasible" stage. They see improvements coming

Figure 6.—NCI Regular Grant Awards, Fiscal Years 1974-80



SOURCE: Office of Technology Assessment from NCI data

from empirical studies that can be applied now or in the near future to treating cancer patients.

There was also a clear division between experts along the lines in which they view cancer treatment. Some who are involved in basic research see the reported improvements in survival rates as limited, at best. In their eyes, research at the most fundamental level is necessary to provide insight and understanding to break away from methods that have changed little over the years. Some experts who argued in support of basic research at the same time voiced support for epidemiology. In their eyes, studying cancer in humans identifies "black boxes" of higher and lower cancer occurrence. Investigating those black boxes is seen as providing opportunities to learn about human cancer.

The other group views the reported improvements as real and clear indications that continual incremental advances will lead to continued betterment of cancer care.

NCI accommodates both points of view, and it funds both types of research. The division between basic and other kinds of research is argued continually.

NCI Staffing

The National Cancer Advisory Board (NCAB) (70) has drawn attention to the fact that NCI staff has not increased in step with its increased budget (see table 25). In particular, the number of personnel declined

Table 24.—Basic and Applied Research and Development Spending at NCI

A. Proportion of budget spent on basic and applied research and development, 1982[a]

	1. Basic	(%)	2. Applied	(%)	3. Development	(%)	Total 1+2+3	(%)
NCI	$328	(33)	$414	(43)	$215	(22)	$958	(100)
Others[b]	$1,491	(61)	$776	(32)	$161	(07)	$2,427	(100)

B. NCI expenditures as a percentage of all NIH[b] expenditures

(18)	(35)	(57)	(2[c])

[a]Dollar amounts are given in millions.
[b]Other institutes not including Fogarty International Center, National Library of Medicine, Office of the Director, Buildings and Facilities.

SOURCE: Office of Technology Assessment from NIH data

Table 25.—Comparison of the Increases in NCI Funding and Changes in the Number of NCI Personnel, Fiscal Years 1971-80

	Dollars			Positions		
Fiscal year	Obligations ($000's)	Percent of increase over base year	Percent of increase over prior year	Actual full-time permanent employees	Percent of increase over base year	Percent of increase over prior year
1971	232,855	(Base year)	—	1,426	(Base year)	—
1972	378,636	62.6%	62.6%	1,665	16.8%	16.8%
1973	431,245	85.2	13.9	1,736	21.7	4.3
1974	581,149	149.6	34.8	1,805	26.6	4.0
1975	699,320	200.3	20.3	1,849	29.7	2.4
1976	760,751	226.7	8.8	1,955	37.1	5.7
1977	814,957	250.0	7.1	1,986	39.3	1.6
1978	872,369	275.0	7.2	1,969	38.1	−0.9
1979	936,696	302.3	7.4	1,973	38.4	0.2
1980	998,047	328.6	6.5	1,837	28.8	−6.7

SOURCE: National Cancer Institute, 1981.

in 1978 and 1980. When a comparison is made between the increase in annual appropriations and the increases in staff, there is a great discrepancy.

The changes in staff positions can also be compared to the 31-percent increase in the NCI budget expressed in constant dollars. When that is done, the 10-percent increase from 1,665 positions in 1972 to 1,837 in 1980 does not seem so out of line.

Making comparisons of positions to inflated dollars or to constant dollars is superficial. Conversations that OTA had with non-NCI experts revealed difference opinions about the number of NCI employees needed. Some NCI grantees (it must be remembered that scientists contacted by OTA were almost all successful grantees) saw little need for more NCI staff. The peer review system (see below) evidently has sufficient staff support, and grantees see little need for NCI consultation or guidance in managing their research projects. The number of competing grant applications received by NCI increased from 1,761 in 1974 to a peak of 2,606 in 1978; it then declined to 2,523 in 1980 (see table 23). Since that number has become relatively stable, no increases appear to be needed in that area. NCI notes, however, that its recent separation of program management activities from review activities will require additional staff for review activities.

Researchers who depend on individual research grants or program project grants (see app. B) appear to favor an NCI largely limited to review, more so than researchers supported mainly by contracts. They believe that standard measures of scientific success—publication in professional journals, invitations to speak to scientific meetings, promotion, etc.—are sufficient to make judgments about a scientist's progress. Objections to increased demands for accountability, which involve reports being submitted to NCI, are frequently expressed. The protests about too many demands for accountability do not extend to financial affairs. Reporting expenditures and surpluses is seen as necessary, but accounting for research results through reports to NCI is seen as unnecessary.

Other experts, particularly those associated with NCI centers, expressed a desire for more NCI senior staff. The additional senior-level personel were seen as being useful in making decisions about the management of the centers' programs and the relationship between NCI and the centers. Some experts also think that the NCI senior-level officials can take a more active role in suggesting or targeting research areas through issuing program announcements or requests for applications in specified areas.

Researchers who run larger enterprises requiring coordination of several investigators, and, especially, clinical research and community outreach programs which have many special rules, favor more expertise at NCI. They believe that decisionmaking and advice from NCI would be improved by more staff.

Furthermore, some experts favored more accountability. Currently each grantee submits a progress report to NCI at the end of each grant year and at the end of the grant period. By general consensus, hardly any of the yearly reports are read by anyone. The response to this observation by some experts is that the annual reports serve no function and should not be required. Others believe that the annual reports should be read and evaluated. The latter procedure would require more NCI staff.

The differing opinions about the value of annual reports illustrate that the number of people needed at NCI depends on what NCI is expected to do. If it is primarily to provide review services to assure that the best research gets funded, it would require a minimum of people in the extramural programs. As NCI gets more involved in aiding in the management

of extramural moneys and in contracts, more people would be required.

Contracts require more NCI supervision, and the General Accounting Office (GAO) (25,26,27,28) has placed part of the blame for poor contract monitoring by NCI on a shortage of personnel. In addition, however, GAO has faulted some aspects of the NCI management system.

In contrast to increased numbers of grants and grant applications, which might require few new staff positions, increased numbers of contract proposals and contracts might require much more staff. Whether or not more staff positions are necessary, then, depends on perceptions of the role of NCI.

Staffing needs of intramural programs appear to be straightforward. The budget allows a certain number of projects; staffing needs are probably directly related to the number of the projects.

No attempt was made in this study to determine the staffing needs of NCI. It seems to be a thorny problem, with experts disagreeing. To some extent the disagreement reflects the relationships that exist between different extramural scientists and the Institute.

ADDENDUM B: QUESTIONS POSED TO EXPERTS BY OTA STAFF

1. What have been the most significant advances in cancer research and applications of research since 1971? What role has NCI played in bringing them about?
2. What have been NCI's most significant advances?
3. In what areas will we likely see breakthroughs in the next decade?
4. What are appropriate yardsticks by which NCI success can be measured? Should we expect to see direct effects of NCI progress in incidence and mortality statistics?
5. What are realistic short- and long-term goals for NCI?
6. Based on today's knowledge, which areas of effort should NCI be emphasizing in the next decade? What areas should be cut back or eliminated?
7. Are there identifiable roadblocks to major breakthroughs in cancer research?
8. Has an appropriate balance been struck between NCI intramural and extramural programs? Between grants to individual researchers and to institutions? Between program project and center grants?
9. Have large NCI center grants to major biomedical research institutions been productive? Is the mechanism for monitoring the performance of such institutions adequate?
10. Can you suggest changes that could be made in NCI management policies that would accelerate progress?
11. Has NCI been successful in technology transfer, as NCI defines it? Have NCI's programs had a positive impact on the community? Are there problems with the mechanism of technology transfer? Are there technologies to be transferred at this time? Are there negative consequences of attempts at technology transfer? What yardsticks can be used to measure success in technology transfer?

ADDENDUM C: EXPERTS CONTACTED BY OTA

Dr. Harold Amos
Harvard Medical School

Dr. David Baltimore
Massachusetts Institute of Technology

Dr. Lester Breslow
UCLA School of Public Health

Dr. Irwin D. J. Bross
Roswell Park Memorial Institute

Dr. Vincent T. DeVita, Jr.
National Cancer Institute

Sir Richard Doll
Oxford University

Dr. Bernard Fisher
University of Pittsburgh School of Medicine

Dr. James F. Fries
Stanford University Medical Center

Dr. Armand Hammer
Occidental International Corporation

Dr. Maureen M. Henderson
University of Washington

Dr. Thomas J. King
Kennedy Institute for Ethics

Mrs. Rose Kushner
Kensington, Maryland

Dr. Joshua Lederberg
The Rockefeller University

Dr. Brian MacMahon
Harvard University School of Public Health

Dr. Elizabeth C. Miller
McArdle Laboratory for Cancer Research

Dr. Marvin Schneiderman
Clement Associates, Inc.

Dr. Guy Newell
M.D. Anderson Hospital & Tumor Institute

Dr. Norton Nelson
New York University

Dr. Henry C. Pitot
McArdle Laboratory for Cancer Research

Dr. David P. Rall
National Institute of Environmental Health Sciences

Dr. Frank Rauscher
American Cancer Society

Dr. Frederick Robbins
Institute of Medicine, National Academy of Sciences

Mr. Benno C. Schmidt
J. H. Whitney & Co.

Dr. Irving J. Selikoff
Mt. Sinai School of Medicine

Dr. Charles Smart
American College of Surgeons

Dr. Howard Temin
McArdle Laboratory for Cancer Research

Dr. Lewis Thomas
Memorial Sloan-Kettering Cancer Center

Dr. Arthur Upton
New York University

Dr. Sidney Wolfe
Public Citizen Health Research Group

Dr. Ernst Wynder
American Health Foundation

Dr. John S. Zapp
American Medical Association

ADDENDUM D: GUIDELINES FOR RECOGNITION OF A CANCER CENTER AS COMPREHENSIVE

These guidelines describe the qualities and characteristics that the National Cancer Advisory Board (NCAB) considers essential for recognition of a cancer center as comprehensive. They will be used by reviewers to evaluate centers that are seeking recognition as new comprehensive centers and also to evaluate established centers to determine the advisability of continued recognition.

In establishing these guidelines, NCAB does not intend that every institution participate in all possible activities relevant to cancer. For example, although one of the requirements for recognition as comprehensive center is the existence of high quality research activities, there is no requirement that *all* research areas be pursued at a given center. Rather, there is the requirement that there be high quality activity in *some* aspects of cancer control and *some* aspects of training, education, and information dissemination. The term comprehensive is intended to convey that the cancer center has high quality activities in each of these major areas, but that within any given area, the center may choose to pursue particular topics and not others.

National and Local Support

The cancer center must have a funded Cancer Center Support (Core) Grant, indicating that center activities are of sufficient quality to achieve funding from the National Cancer Program. In addition, there must be evidence of material support for center activities from the parent institution(s) and the local community.

Research Activities

The cancer center should support laboratory, clinical, epidemiologic, and evaluative research efforts of

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the highest quality and should create an environment which fosters cancer-related information exchange, cooperation, and collaboration between laboratory scientists of multiple disciplines and between laboratory scientists, clinical scientists, and epidemiologists. Centers should maintain their own clinical investigative activities. Those activities should include participation in regional and/or national clinical trials related to the cancers being studied by the center in question. The center should have available the personnel and facilities to carry out high quality diagnostic, therapeutic, and rehabilitative procedures in the interdisciplinary setting most suited to the cancers being investigated. The center should make a commitment to participate in uniform clinical data acquisition and reporting through the Centralized Cancer Patient Data System (CCPDS).

Cancer Control Activities

The cancer center should serve as an important focal point for local and regional programs designed to control cancer through research and demonstration activities in areas such as prevention, detection, diagnosis, treatment, and rehabilitation. The center should seek the active participation of all sectors of the professional and lay community in control activities.

Training, Education, and Information Dissemination

The cancer center should serve as an important focal point for local and regional information dissemination, as well as for professional and lay education programs. Programs to assess which methods of information dissemination and education effectively modify professional and lay behavior patterns are desirable. Centers should also be actively involved in training of professional and support personnel.

Administration

The cancer center (or in the case of consortia, the constituent institutions) should have a formal commitment of support from the parent institution(s), manifested by the center director having the following: 1) primary control of space and equipment; 2) necessary control over professional and staff appointments to enable the center director to effectively direct the center and assure accomplishment of its mission; 3) control of grouped beds and ambulatory facilities for clinical cancer research; and 4) responsibility for program planning, evaluation, and implementation, preparation of budgets and control of expenditures. In addition, the center must have an administrative structure that will assure long-term viability, efficiency of operation, and sound financial practice.

Geographic Impact

Scientific excellence of any center is a primary consideration. The geographic location of the cancer center, however, should increase the national capability to carry out regional training, education and information dissemination activities. The location of other comprehensive centers and the size of the regional population with access to the center are additional factors bearing on recognition.

Chapter 7

Technology Transfer at the National Heart, Lung, and Blood Institute

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Chapter 7

Technology Transfer at the National Heart, Lung, and Blood Institute

INTRODUCTION

Diseases of the cardiovascular and respiratory systems account for 5 of the 10 leading causes of death in the United States. Four of these are chronic diseases under study by the National Heart, Lung, and Blood Institute (NHLBI)—heart disease (ranked first), cerebrovascular disease (third), chronic obstructive lung disease (fifth), and arteriosclerosis (ninth) (see table 26). Moreover, hypertension and heart conditions are among the 10 leading chronic causes of morbidity (see table 27); and cardiovascular diseases account for nearly 5 million hospitalizations, with an average length of stay of over 10 days (table 28), and over 55 million physician office visits (table 29).

Although cardiovascular diseases remain the number one cause of mortality, there has been a continuing decline in age-adjusted mortality rates since the 1960's, including a 25-percent decline between 1968 and 1978 (see figs. 7, 8, and 9). This decrease in mortality from cardiovascular diseases has been attributed to advances in diagnosis and treatment, preventive measures, and changes in lifestyle. The decline has not been confined to the United States, but

Table 27.—Morbidity From Selected Chronic Conditions, United States, 1979 (thousands)

Condition	Prevalence
1. Chronic sinusitis	28,054
2. Arthritis	25,868
3. Hypertension	23,745
4. Absence of extremities (or parts), deformities, orthopedic impairments	20,213
5. Hearing impairments	16,663
6. Heart conditions	16,428
7. Hay fever (without asthma)	15,620
8. Digestive conditions	14,692
9. Hemorrhoids	8,813
10. Eczema, dermatitis, urticaria	7,754
11. Chronic bronchitis	7,474
12. Corns, callosities, bunion	6,584
13. Acne	6,450
14. Asthma (with or without hay fever)	6,402
15. Varicose veins	6,030
16. Diseases of the urinary system	5,602
17. Migraine	5,348
18. Diabetes	5,236
19. Synovitis, bursitis, tenosynovitis	4,637
20. Diseases of nail	4,302

SOURCE: National Institutes of Health, derived from unpublished data from the National Center for Health Statistics

Table 26.—Mortality From the Ten Leading Causes of Death, United States, 1979[a]

Cause of death	Number	Rate per 100,000 population	Percent
Total	1,895,380	866.2	100.0
1. Heart disease	723,100	330.4	38.2
2. Malignant neoplasms	401,450	183.5	21.2
3. Cerebrovascular diseases	167,320	76.5	8.8
4. Accidents	102,740	47.0	5.4
5. Chronic obstructive pulmonary disease	49,580	22.7	2.6
6. Influenza and pneumonia	43,770	20.0	2.3
7. Diabetes	32,780	15.0	1.7
8. Cirrhosis of the liver	29,620	13.5	1.6
9. Atherosclerosis	28,410	13.0	1.5
10. Suicides	25,710	11.7	1.4
All other causes	290,900	132.9	15.3

[a]Based on a 10-percent sample of death certificates for the 12 months of 1979. Causes of death were coded to the Ninth Revision of the International Classification of Diseases.

SOURCE: National Center for Health Statistics, *Monthly Vital Statistics Report* 29:1, Apr. 9, 1980.

Table 28.—Number of Hospital Discharges and Days for Patients With Cardiovascular Diseases, United States, 1978

First-listed diagnosis and ICDA code	Number of discharges (thousands)	Length of stay (days)	Number of days (thousands)
Total cardiovascular 390–458, 746, 747	4,828	10.2	49,163
Rheumatic fever and rheumatic heart disease 390–398	114	10.8	1,235
Acute myocardial infarction 410	425	12.5	5,320
Other coronary heart disease 411–413	1,529	9.1	13,989
Hypertensive disease 400–404	317	6.8	2,168
Cerebrovascular disease 430–438	648	13.4	8,700
Congenital heart disease 746, 747	62	7.7	479
Other cardiovascular diseases 420–429, 440–458	1,733	10.0	17,268

SOURCE: National Heart, Lung, and Blood Institute, based on unpublished data from the Hospital Discharge Survey, National Center for Health Statistics.

Table 29.—Number and Percent Distribution of Physicians' Office Visits for Diseases of the Circulatory System and for Selected Principal Diagnoses, United States, 1978

Diagnosis and ICDA code	Number of visits (thousands)	
Total circulatory 390–458	55,167	
Rheumatic fever and rheumatic heart disease 390–398	1,000	
Hypertensive disease 400–404	24,968[a]	
Essential benign hypertension 401		24,068
Ischemic heart disease 410–413	14,578	
Acute myocardial infarction and other acute IHD 410-411		1,610
Chronic IHD 412		11,295
Angina pectoris 413		1,674
Other forms of heart disease 420–429	4,378	
Symptomatic heart disease 427		3,314
Cerebrovascular disease 430–438	2,270	
Diseases of arteries, arterioles, capillaries 440–448	2,190	
Arteriosclerosis 440		740
Diseases of veins and other circulatory 450–458	5,764	
Phlebitis and thrombophlebitis 451		1,221
Varicose veins of lower extremities 454		988
Hemorrhoids 455		1,855

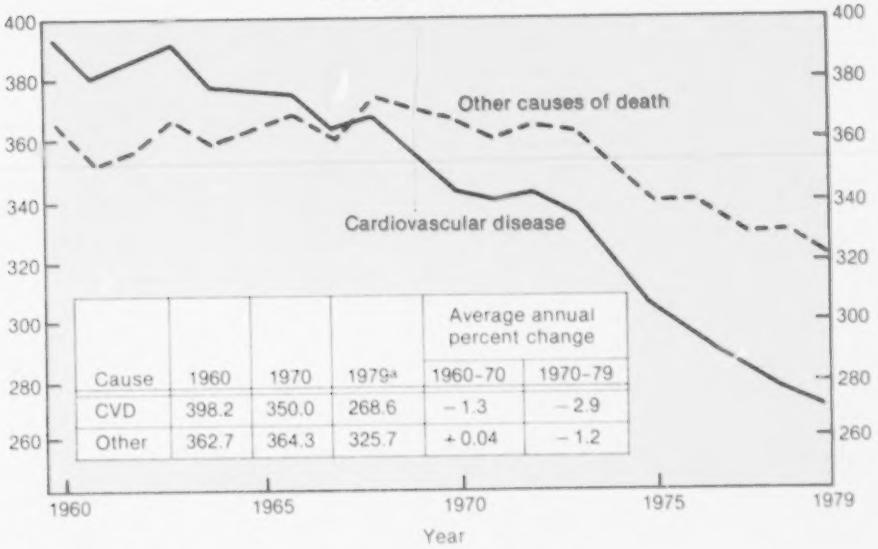
[a]An estimate of 51 million is given by the National Disease and Therapeutic Index, which includes visits in all locations (office, hospital, etc.) and by telephone.

SOURCE: National Heart, Lung, and Blood Institute, based on unpublished data from the National Ambulatory Medical Care Survey, National Center for Health Statistics.

has also occurred in Canada, Australia, and Finland, countries that also have high coronary artery disease death rates. In England, however, where preventive care in nutrition and hypertension treatment have not been vigorously pursued, mortality from heart disease has remained constant. In 1968, a middle-aged male American had a 40-percent higher risk of death than an Englishman; by 1976 the American's risk had fallen below the Englishman's (37,40).

Improvements in rates of mortality and morbidity are not only desirable from a human well-being standpoint. There are also large economic implications. The economic cost in the United States of death due to circulatory, respiratory, and blood diseases was estimated at close to $40 billion, in terms of lost earnings (43). In fact, diseases of the circulatory system rank first among all diseases in economic costs of death (accidents are first overall). These diseases also rank first in total amount of disability (measured in number of days) caused by disease, in total economic cost of morbidity (productivity losses), and in overall totals of the economic "burden" of diseases, including the above meas-

Figure 7.—Death Rates for Cardiovascular Diseases and Other Causes of Death, United States, 1960-79



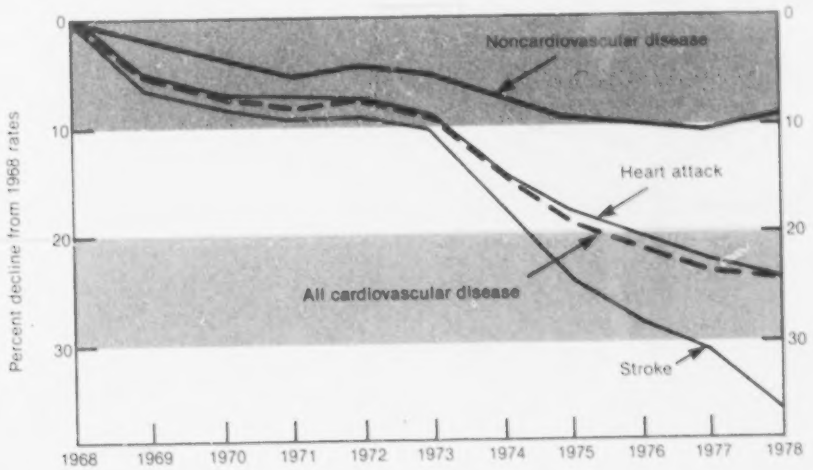
Cause	1960	1970	1979[a]	Average annual percent change 1960-70	Average annual percent change 1970-79
CVD	398.2	350.0	268.6	−1.3	−2.9
Other	362.7	364.3	325.7	+0.04	−1.2

NOTE: Age-adjusted to U.S. population, 1940.

[a]Estimated by NHLBI.

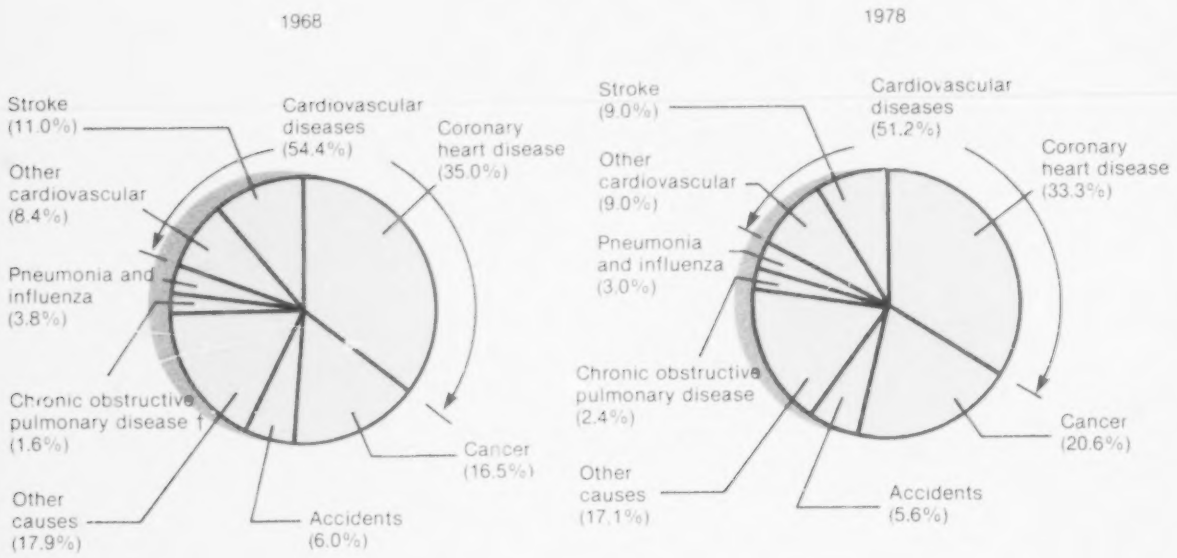
SOURCE: Prepared by the National Heart, Lung, and Blood Institute. Data from the National Center for Health Statistics.

Figure 8.—Trends in Cardiovascular Disease and Noncardiovascular Disease: Decline by Age-Adjusted Death Rates, 1968-78



SOURCE: National Heart, Lung, and Blood Institute.

Figure 9.—Deaths by Cause and Percentage of Total Deaths, 1968 and 1978



SOURCE: National Heart, Lung, and Blood Institute

ures and others such as health care expenditures (43).

Improvement in treated cases through the combined impact of medical and surgical interventions (e.g., coronary bypass surgery, coronary care units, emergency medical services) cannot account for the 25-percent decline in age-adjusted mortality rates in the 1970's. The suggestion, therefore, is that the incidence and severity of the disease have decreased. Among the factors cited are greater awareness of overnutrition, increased physical activity, decreased smoking, and treatment of hypertension. On the latter factor (37):

> The proportion of hypertensive persons under treatment has doubled in recent years . . . More effective use of antihypertensive agents could be responsible for perhaps a third of the reduction in cardiovascular mortality . . . Evidence that hypertension control is an important contributor to the decline is especially strong because hypertension is one of the major risk factors for stroke, cardiac failure, and coronary disease; hypertension-related deaths have shown the steepest decline; and declines in stroke incidence are seen in women who have shown the greatest improvement in hypertension awareness and treatment (references omitted).

A review of the history and development of NHLBI would show a concurrent expansion in its functions and funding at the same time these decreases in cardiovascular disease mortality rates were occurring. Determination of a cause-and-effect relationship between the rise of NHLBI and improvement in cardiovascular mortality is not possible. However, as the leading research organization against cardiovascular disease, NHLBI influences the direction of research, development, and application of the instruments against cardiovascular disease, and for the past 10 years, it has operated under explicit legislative mandates in technology transfer. Thus, this summary of how NHLBI carries out its technology transfer responsibilities focuses on: 1) the administrative structure that

NHLBI has developed for technology transfer, and 2) the kinds of technology transfer activities it has supported to identify whether these activities have been in concert with the factors that are known to have helped to lower cardiovascular disease mortality rates.

HISTORY AND DEVELOPMENT OF TECHNOLOGY TRANSFER AT NHLBI

The National Heart Institute was established in 1948 under the National Heart Act (Public Law 80-755). In 1969, it was designated the National Heart and Lung Institute to reflect its expanded responsibilities in diseases of the lung. And in 1976, its research responsibilities were recognized to include "the use of blood and blood products and the management of blood resources," and the institute was redesignated the National Heart, Lung, and Blood Institute.

Apart from these laws, which recognized NHLBI's role in heart, lung, and blood diseases, the National Heart, Blood Vessel, Lung, and Blood Act of 1972 (Public Law 92-423) has most influenced NHLBI's current role. First, the 1972 legislation established separate funding and renewal periods for NHLBI, as had been established for the National Cancer Institute (NCI) in the previous year (1971). In contrast, the other institutes of the National Institutes of Health (NIH) fall under the general research authority of the Public Health Service Act, which places no specific disease category allocations nor time limits on their authorization. Second, the 1972 act specified the following responsibilities for NHLBI:

- research into the epidemiology, etiology, and prevention of heart, blood vessel, lung, and blood diseases, including the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences;
- research in the basic biological processes and mechanisms of the heart, blood vessel, lung, and blood;
- development and evaluation of the techniques, drugs, and devices used in the diagnosis and treatment of these diseases;
- programs to develop technological devices to assist, replace, or monitor vital organs;
- programs for field studies and large-scale testing, evaluation, and demonstration of approaches to these diseases;
- research in blood diseases and the use of blood resources;
- education and training of scientists, clinicians, and educators in these fields;
- public and professional education in these diseases;
- programs for research of these diseases in children; and
- programs for research, development, demonstration, and evaluation in emergency medical services.

The 1972 act also specified that:

- an Assistant Director for Health Information Programs be appointed to provide the public and health professionals with information on these diseases. Special emphasis was to be placed on disseminating information regarding diet, exercise, stress, hypertension, cigarette smoking, weight control, and other factors related to prevention;
- prevention and control programs be established with other governmental and private health agencies;
- national research and demonstration centers be established in these diseases;
- an interagency technical committee be established to coordinate Federal health programs and activities in these diseases; and
- no less than 15 percent of appropriated funds be used for programs in lung diseases, and 15 percent in programs for blood diseases and blood resources.

Finally, the 1972 act required annual reports summarizing that year's accomplishments and plans for the next 5 years from the director of the institute and from NHLBI's National Advisory Council.

In 1974, NHLBI divided its activities into program efforts in: 1) research, and 2) prevention, control, and education (72):

> The Research programs deal largely with the development of new knowledge and the testing and evaluation of existing knowledge. The Prevention, Control, and Education programs deal with the application and dissemination of knowledge already developed and evaluated through research, but not yet effectively applied toward the prevention, control, and treatment of disease. These Prevention, Control, and Education programs are an essential link between biomedical research and health care. Their purpose is not to deliver health services but rather to improve and expedite the transmission of fundamental research advances to the public and to medical practitioners and thereby help to promote the health of our citizens.

The research and prevention, control, and education activities were to be coordinated within a broad program strategy by (72):

- initiating an ordered sequence of coordinated program activities ranging from the acquisition of new knowledge to demonstration and control programs in the health care setting of the community;
- providing adequate program evaluation before the application of existing knowledge to health care delivery systems; and
- evaluating the impact of implemented programs on the health of the American people.

This program strategy was to be applied to subcategories or elements of heart and vascular diseases, lung diseases, and blood diseases and blood resources. The initial elements have remained the same for the Division of Heart and Vascular Diseases and undergone minor modifications in the Divisions of Lung Diseases and of Blood Diseases and Resources. Current NHLBI program elements by division are summarized in table 30.

The organizational structure of NHLBI is summarized in figure 10, and total appropriations are summarized in table 31. Fiscal year 1982 marks the second time that NHLBI appropriations have not increased in actual dollars.

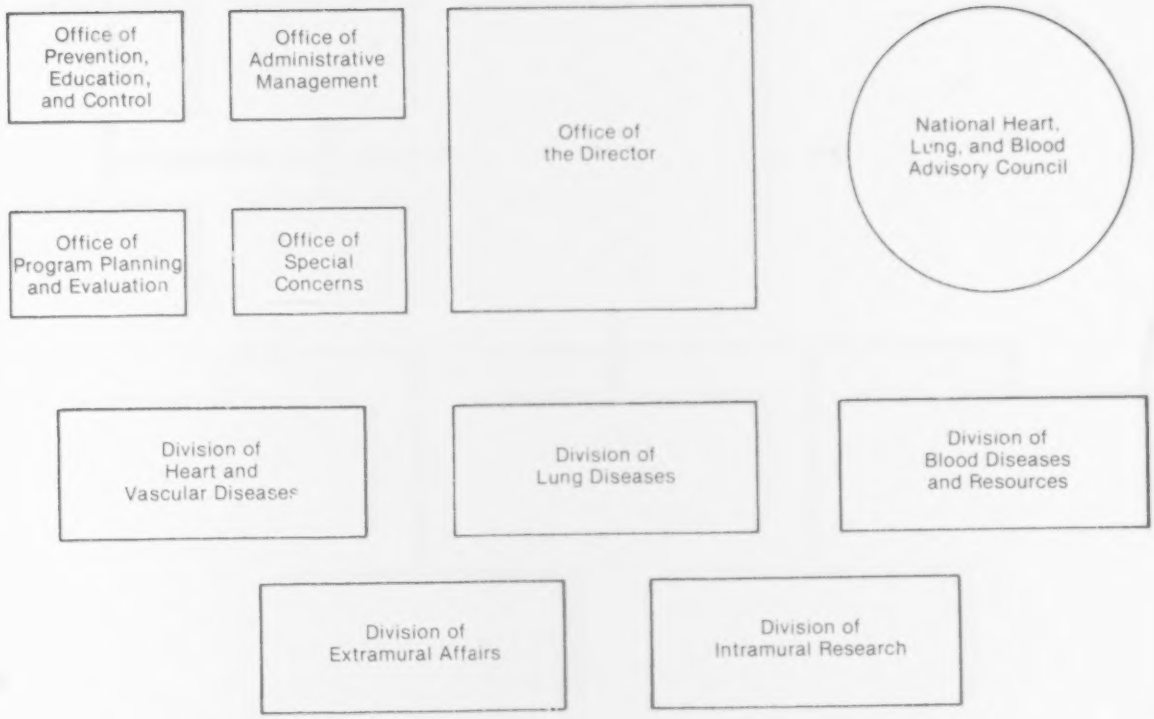
Because of overlapping responsibilities between the organizational components shown in figure 10 (e.g., extramural and intramural research takes place in all three of the categorized disease divisions), allocation of these funds among NHLBI's various activities can be expressed in various parameters. For example, table 32 summarizes 1980 funds as allocated among: 1) extramural research in heart and vascular diseases, lung diseases, and blood diseases

Table 30.—NHLBI Program Elements by Division

Division of Heart and Vascular Diseases	Division of Lung Diseases	Division of Blood Diseases and Resources
Arteriosclerosis	Structure and function of the lung	Bleeding and clotting disorders
Hypertension		Red blood cell disorders
Cerebrovascular disease	Chronic obstructive lung diseases	Sickle cell disease
Coronary heart disease	Pediatric pulmonary disease	Blood resources
Peripheral vascular disease	Fibrotic and immunologic interstitial lung diseases	
Arrhythmias	Respiratory failure	
Heart failure and shock	Pulmonary vascular diseases	
Congenital and rheumatic heart disease		
Cardiomyopathies and infections of the heart		
Circulatory assistance		

SOURCE: National Heart, Lung, and Blood Institute.

Figure 10.—NHLBI Organizational Structure


Office of Prevention, Education, and Control
Office of Administrative Management
Office of the Director
National Heart, Lung, and Blood Advisory Council
Office of Program Planning and Evaluation
Office of Special Concerns
Division of Heart and Vascular Diseases
Division of Lung Diseases
Division of Blood Diseases and Resources
Division of Extramural Affairs
Division of Intramural Research

SOURCE: National Heart, Lung, and Blood Institute

Table 31.—NHLBI Appropriations, Fiscal Years 1972-82 (dollars in thousands)

1972	$224,302
1973	290,784
1974	289,550
1975	324,630
1976	370,013
1977	396,661
1978	447,909
1979	510,134
1980	527,488
1981	560,264
1982	559,637

SOURCE: National Institutes of Health

and resources; 2) intramural research; 3) direct operations; and 4) program management. Table 33 summarizes 1982 funds in similar fashion, but with extramural research categorized by research grants (see the table for further subclassification), research and development contracts, and training.

NHLBI uses yet another method of categorizing its funding in the 5-year planning requirements of its annual reports. Extramural research is subclassified into: 1) heart and vascular diseases; 2) lung diseases; 3) blood diseases and resources; 4) national research and demonstration centers; 5) prevention, education, and control programs; 6) training; and 7) construction. Table 34 summarizes NHLBI's 1980 projections for 1982, using these categories of extramural research. (The reader should compare the categories in table 34 with those in tables 32 and 33. Also note that the actual appropriations for 1982 were $559.6 million, in contrast to projected needs of $732.4 million or a lowerbound esti-

Table 32.—NHLBI Appropriations, Fiscal Year 1980 (dollars in thousands)

		Grants and contracts					
		R&D grants			R&D	Research training	
	Total	Projects	Centers	Others	contracts	Individuals	Institutions
Extramural research:							
Heart and vascular diseases	$309,913	176,545	33,568	11,479	67,942	3,107	17,272
Lung diseases	75,199	44,866	14,022	4,377	4,817	782	6,335
Blood diseases and resources	72,345	45,485	14,716	1,452	6,232	993	3,467
Intramural research	39,040	—	—	—	—	—	—
Direct operations	25,062	—	—	—	—	—	—
Program management	5,532	—	—	—	—	—	—
Total	$527,091	266,896	62,306	17,308	78,991	4,882	27,074

SOURCE: National Institutes of Health

Table 33.—NHLBI Appropriations, Fiscal Year 1982 (dollars in thousands)

Research grants	
Research projects:	
Noncompeting projects	$211,293
Administrative supplements	1,455
Competing projects:	
Competing renewals	46,007
New	42,672
Supplemental	2,932
Subtotal, competing projects	91,611
Subtotal, research projects	304,359
Research centers	64,808
Other research:	
Research career programs	14,476
Cooperative clinical research	4,838
Minority biomedical support	2,112
Other research related	2,178
Subtotal, other research	23,604
Total, research grants	392,771
Training	
Individual awards	4,826
Institutional awards	22,948
Total, training	27,774
Research and development contracts	$56,050
Intramural research	48,442
Direct operations	28,100
Management fund	(26,293)
Program management	6,500
Total	$559,637

SOURCE: National Institutes of Health

Table 34.—1980 NHLBI Projected Resource Allocation[a] for Fiscal Year 1982 (dollars in millions)

	Allocation	Lowerbound allocation
Extramural research programs:		
Heart and vascular diseases	$294.2	$283.2
Lung diseases	79.2	75.8
Blood diseases and resources	85.5	79.6
National research and demonstration centers	50.5	14.6
Prevention, education, and control	60.0	49.1
Training	55.0	45.0
Construction	0.0	0.0
Total extramural research programs	$624.4	$643.4
Intramural research	56.5	50.0
Direct operations and program management	51.4	46.1
Total	$732.4	$643.4

NOTE: The figures in this table were not the actual appropriations. The table is used to illustrate the various ways allocations can be made. See text for explanation.

[a]Tabulations give the primary thrust of activities, even though the activities generally involve more than one subprogram.

SOURCE: NHLBI 8th Annual Report, 1980.

mate of $643.4 million. Projected needs have always been higher than actual appropriations.)

NHLBI is not the only Federal agency funding cardiovascular, lung, and blood research. This was recognized in the 1972 act through the requirement that an Interagency Technical Committee (IATC) be established to coordinate Federal health programs and activities in the cardiovascular, lung, and blood areas. The Director of NHLBI chairs the committee, which includes representatives from all Federal departments and agencies whose programs involve health functions or responsibilities. IATC's first report was issued in 1977, and an update was provided in 1979.

In fiscal year 1979, NHLBI provided 63.8 percent of Federal funds, with other NIH institutes

providing 20.7 percent, and other Federal programs providing the remaining 15.5 percent. Figure 11 summarizes the distribution of funds according to disease categories, and figure 12 summarizes the distribution of funds according to the program elements of NHLBI's three divisions. These Federal funds were being used to support nearly 9,000 research projects in fiscal year 1979 (77).

In implementing its program strategy of initiating an ordered sequence of coordinated program activities, providing adequate program evaluation before application to health care, and evaluating the impact of implemented programs (i.e., NHLBI's program strategy response to the 1972 act), NHLBI conceptualizes the biomedical research spectrum as illustrated in figure 13. NHLBI considers the research spectrum from basic research to demonstration programs (fig. 13) as comprising the initial knowledge development phase of the technology transfer process (i.e. the scientific data base shown in fig. 14).

NIH's research institutes have the primary responsibility for knowledge development and the technical analysis phase of the judgment and decision steps in the technology transfer process (fig. 14), with the NIH Director's Office playing an increasing role as the technology moves toward specific nonscientific issues. NHLBI, because of its broad mandate, not only may take responsibility for technical analyses, but also may play a lead role in interface assessment and knowledge dissemination (76).

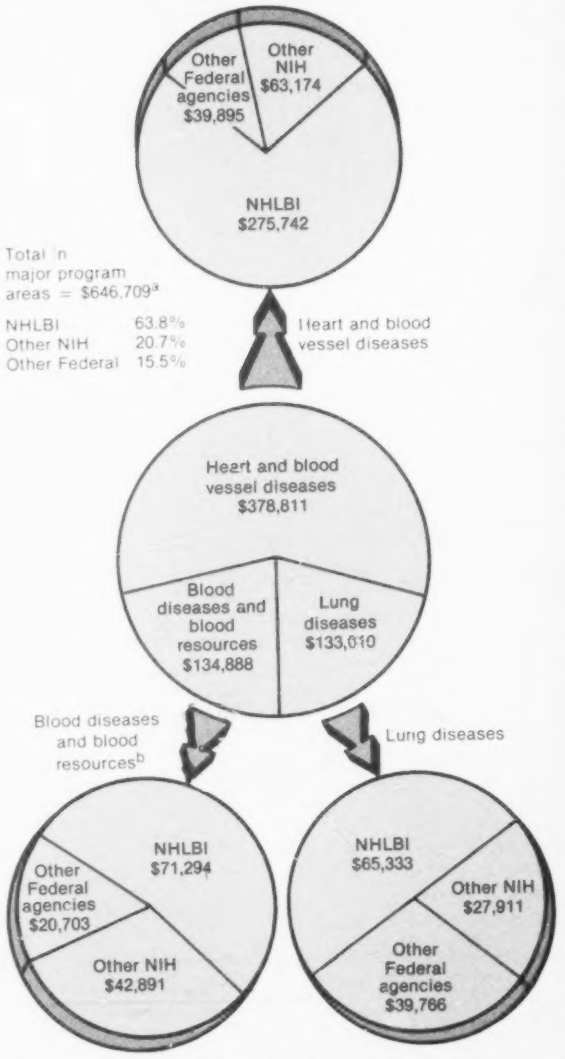
NHLBI created a Technical Consensus Development Committee in 1977, which adopted the following goal (76):

> To promote prompt adoption into practice of approaches that are technically valid, socially and ethically acceptable, and economically feasible, for prevention or control of heart, lung and blood diseases.

The Committee, which meets periodically, has the following agenda (76):

1. definition of process itself, and interaction with planning and evaluation systems already in place;
2. development of criteria for determining consensus candidates;
3. development of criteria for determining relative priorities of consensus candidates;
4. formulation of a tracking system for technology consensus projects; and
5. designation of specific points at which to hold consensus exercises (e.g., completion of a clinical trial).

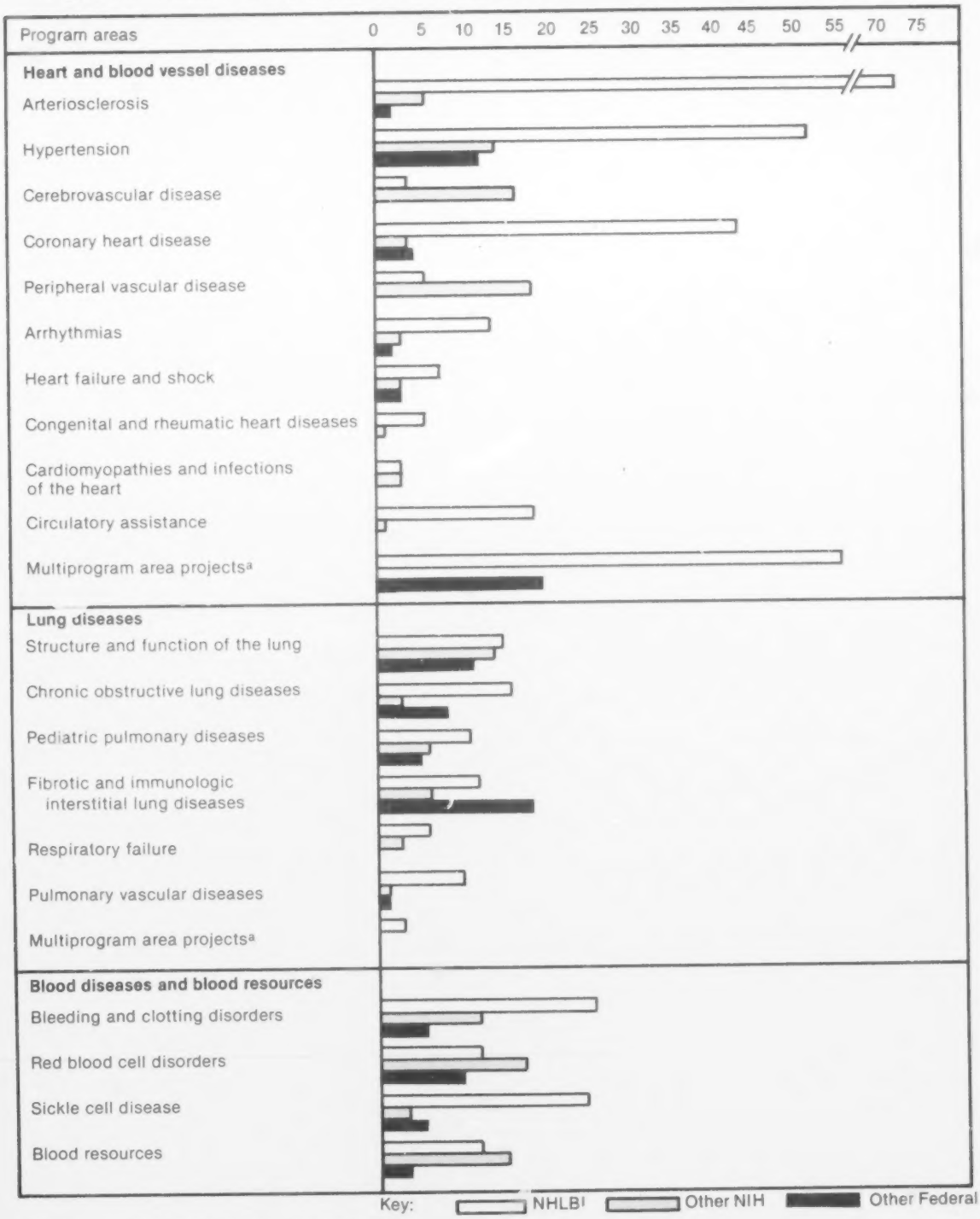
Figure 11.—Distribution of Fiscal Year 1979 Funding Among Federal Agencies by Major Areas of the National Program (dollars in thousands)



[a]Total does not include unavailable funding data indicated in tables.
[b]Does not include any projects directly related to leukemias, blood cell formation, or the cellular immune system, but only those directly related to blood diseases and blood resources.

SOURCE: National Heart, Lung, and Blood Institute.

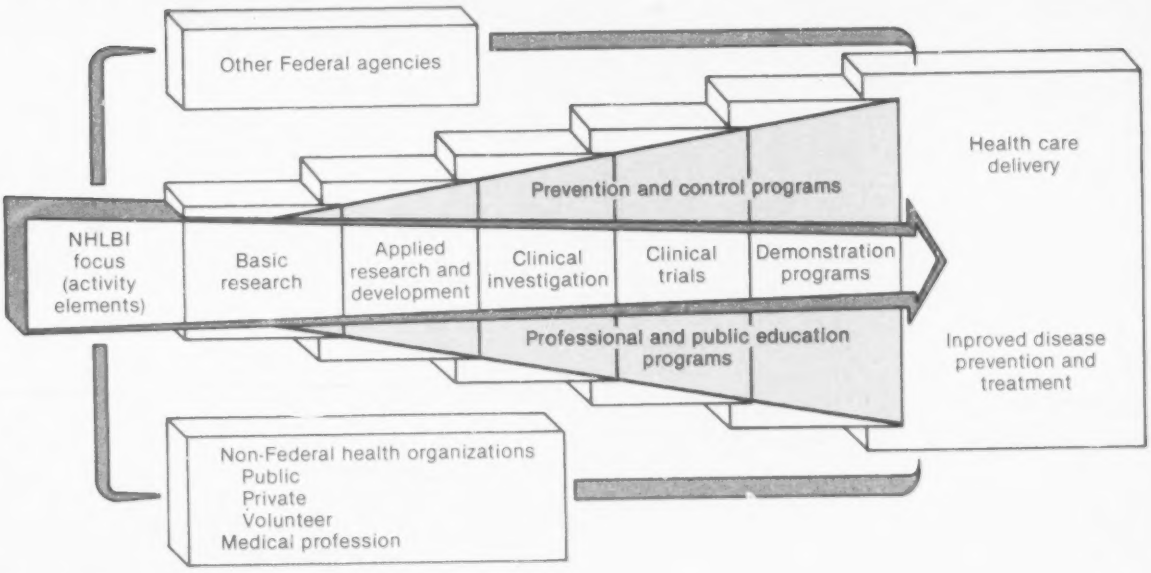
Figure 12.—Fiscal Year 1979 Federal Funding Totals by National Program Area (dollars in millions)



[a]Projects which are directly related to more than one National Program area.

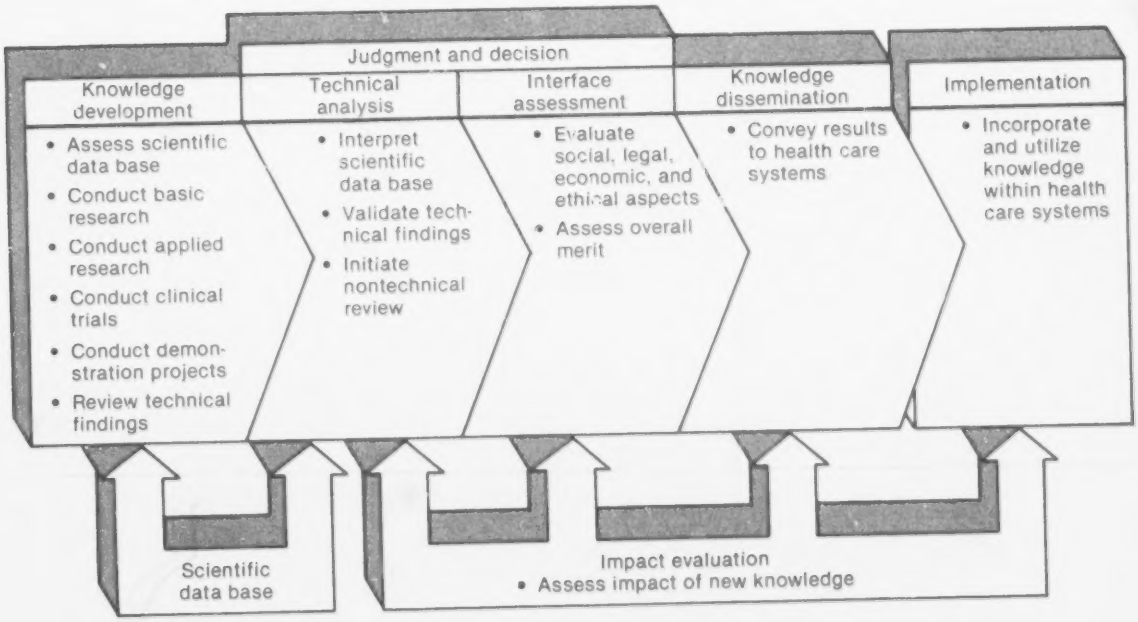
SOURCE: National Heart, Lung, and Blood Institute.

Figure 13.—NHLBI's Conception of the Biomedical Research Spectrum



SOURCE: National Heart, Lung, and Blood Institute.

Figure 14.—NHLBI's Conception of the Technology Transfer Process


Judgment and decision
Knowledge development
Technical analysis
Interface assessment
Knowledge dissemination
Implementation
• Assess scientific data base
• Conduct basic research
• Conduct applied research
• Conduct clinical trials
• Conduct demonstration projects
• Review technical findings
• Interpret scientific data base
• Validate technical findings
• Initiate nontechnical review
• Evaluate social, legal, economic, and ethical aspects
• Assess overall merit
• Convey results to health care systems
• Incorporate and utilize knowledge within health care systems
Scientific data base
Impact evaluation
• Assess impact of new knowledge

SOURCE: National Heart, Lung, and Blood Institute.

NHLBI technology transfer activities are followed by a coordinator in the Office of Program Planning and Evaluation. In 1978, concurrent with the establishment of the Office for Medical Applications of Research (OMAR) in the NIH Director's Office, NHLBI organized its own Medical Applications Program (MAP) in the Office of Program Planning and Evaluation. The MAP coordinator has the following resources available: 1) ad hoc MAP-Staff Working Groups selected from NHLBI's divisions and offices, 2) IATC, and 3) an NHLBI Advisory Council Working Group for Medical Applications.

MAP has two related but functionally separate sets of objectives. First are medical applications objectives incorporated within the program plans for each of the NHLBI operating units. Second are objectives at the level of the NHLBI Director's Office. The latter objectives are (75):

1. serve as a current source for an inventory and status information on all high priority "technologies in transition," as identified and prioritized by NHLBI operating units.
2. insure coordination of technology development, assessment, and dissemination within NHLBI and between NHLBI and other portions of NIH or external agencies.
3. assist NHLBI operating units in providing visibility to their medical applications plans and accomplishment.
4. assist NHLBI operating units in maintaining awareness of advances in the state-of-the-science in technology assessment, technology validation, dissemination of technology developments to the clinical community, and diffusion of biomedical advances into standard clinical practice.
5. insure that a system for identifying and acting on priority technologies is incorporated into NHLBI's planning process.

These plans are still under formulation within NHLBI, with the assistance of a consultant from the Sloan School of Management at the Massachusetts Institute of Technology. However, the MAP objectives remain the same, with the overall program strategy still to be worked out.

The first objective is to serve as a source for an inventory and status information on high priority technologies—classified as emerging, new, or established technologies in transition—which NHLBI is actually developing or for which formal evaluations are planned or underway.

An emerging technologies list was generated by the divisions of NHLBI in 1979. This list (see table 35) was part of a list of several hundred technologies compiled by the Public Health Service Agencies for the (at that time) newly legislated National Center for Health Care Technology (NCHCT). However, the criteria for inclusion were considered too vague, and the pur-

Table 35.—Emerging Technologies Identified by the NHLBI Divisions in 1979

Heart Division
Clinical trials
Hypertension detection and followup program (HDFP)
Aspirin myocardial infarction study (AMIS)
Multicenter investigation of limitation of infarct size (MILIS)
Coronary artery surgery study (CASS)
Indomethacin v. surgery for patent ductus
Multiple risk factor intervention trial (MRFIT)
Cholestyramine to reduce lipids
Beta-blocker heart attack trial (BHAT)
Diagnostic/therapeutic technology
Methods for quantifying infarct size
Percutaneous transluminal coronary angioplasty (PTCA)
Circulatory assist devices
Long term
Noninvasive detection of atherosclerotic lesions
Totally implantable circulatory assist devices
Blood Division
Prenatal diagnosis of hemophilia
Prenatal diagnosis of thalassemia
Prenatal diagnosis of sickle cell syndrome
Antiplatelet agents for arterial thrombosis
Fibrinolytic agents
Prophylaxis for deep vein thrombosis (DVT)
Two new iron chelators tested in animals
Activated factor IX for hemophiliacs
Extracorporeal carbamylation of hemoglobin in sickle cell disease
Granulocyte transfusions
Plasmapheresis and cytapheresis
Fluorocarbons as blood substitutes
Lung Division
Noninvasive assessment of pulmonary hypertension
Noninvasive methods to monitor intracellular events
Noninvasive diagnosis of pulmonary embolism

SOURCE: National Heart, Lung, and Blood Institute.

pose of compiling the list was not clear. Thus, in 1980, NHLBI defined an "emerging health care technology" as:

> . . . any technology under development that appears likely to be used in the practice of medicine within five years. This implies that the technology has passed a critical point in the development process such that validation of safety and efficacy in human subjects either has been initiated or is imminent.

NHLBI also set forth the following criteria for priority identification of emerging technologies: 1) potential benefit; 2) health risk; or 3) current or potential social, ethical, legal, or economic concerns. Finally, NHLBI identified the following uses for the emerging technology list (73):

1. monitoring of the diffusion/development process;
2. acceleration of development efforts;
3. conduct of additional validation studies;
4. analysis of the state of the science;
5. development of specific assessments from certain perspectives such as potential ethical, legal, or economic impact;
6. development of multifaceted assessments;
7. initiating consensus development;
8. development of a strategy for assessing third-party reimbursement recommendations;
9. dissemination of information for health planning;
10. general dissemination of information (pro or con); and/or
11. planning for impact evaluation.

The criteria mentioned above led to a much smaller list of emerging technologies in the 1980 NHLBI compilation. This list (see table 36) included eight emerging technologies, only four of which had been on the 1979 list.

In NHLBI's current compilation, in addition to emerging technologies, new technologies and established technologies in transition are also to be identified (75). Thus, some technologies on the 1979 list should appear under one of these two categories—e.g., coronary artery surgery (46) and beta-blockers for heart attacks (8).

New technologies are "those that may have passed the stage of clinical trials but are not yet widely disseminated, or those that are moving into wide scale usage without benefit of clinical trials." Priority for identifying new technologies is given to "those which affect large population groups, represent major advances in terms of improved outcomes, have critical unanswered safety issues, and have significant economic implications."

Established technologies in transition are "those established technologies currently undergoing or likely to undergo major changes in their extent of usage or costs as a result of new research findings, or for which serious concerns have been raised concerning safety or effectiveness." Priority is to be given to "those that are the most widely used, have the greatest economic implications, or pose grave concerns for patient safety, and for which significant NHLBI resources are currently, or are planned, to be directed at developing or disseminating new knowledge, or in changing the degree to which the technology is applied."

The year 1982 marked the 10th anniversary of the National Heart, Blood Vessel, Lung, and Blood Act of 1972, and NHLBI is currently compiling a list of the most important clinical advances of the past 10 years. Thus, three lists are being compiled: 1) emerging technologies; 2) more established technologies which warrant reexamination (new technologies and established technologies in transition); and 3) the most important clinical advances of the past 10 years.

Table 36.—Emerging Technologies, NHLBI, 1980 Compilation

Therapeutic technologies
Percutaneous transluminal coronary angioplasty[a]
Circulatory assist devices[a]
High frequency ventilation
Therapeutic plasmapheresis[a]
Diagnostic technologies
Ultrasound B-sound imaging
Subtraction radiography
Measurement of high density lipoprotein
Prenatal diagnosis of sickle cell disease[a]

[a]Technologies which were on the 1979 list.

SOURCE: National Heart, Lung, and Blood Institute.

TECHNOLOGY TRANSFER ACTIVITIES

NHLBI has sponsored four consensus development meetings for OMAR in the NIH Director's Office: 1) transfusion therapy in pregnant sickle cell disease patients (April 1979); 2) improving clinical and consumer use of blood pressure measuring devices (April 1979); 3) thrombolytic therapy in thrombosis (April 1980); and 4) coronary bypass surgery (December 1980).

Since technology transfer involves the translation of basic research into effective and appropriate treatment, management, or prevention of diseases, much of what NHLBI supports is part of the technology transfer process. More specifically, the later stages of knowledge development—clinical trials and demonstration programs—are already far down the path toward a technology's incorporation into direct health care delivery and educational programs for the prevention of diseases. In fact, NHLBI has explicitly recognized the technology transfer functions of clinical trials and demonstration programs:

> The large-scale collaborative study or clinical trial has become an important, indeed, critical activity in the biomedical research spectrum. It is the clinical trial that determines most precisely the efficacy of treatment or preventive regimens. These large studies, which may cost tens of millions of dollars, impact both on research and medical practice. In testing hypotheses born from fundamental and clinical research they can point toward research areas where more work is required and where the results will have the most widespread benefit. They have the potential to improve the quality of health care and control costs through their careful comparison of alternative treatments (42).

> Demonstration programs test methods to introduce or facilitate delivering health care advances to the public. Demonstration activities, which are a recent addition to the Institute's programs, have been implemented to effectively translate research findings into health practices. Such programs will be of even greater importance as more clinically applicable information becomes available for dissemination from ongoing clinical trials (79).

Thus, NHLBI's technology transfer activities consist of clinical trials and demonstration programs which "deal with the application and dissemination of knowledge already developed and evaluated through research, but not yet effectively applied toward the prevention, control, and treatment of disease" (72). The technology transfer process previously described might be thought of as NHLBI's method of managing these activities as they apply to specific technologies.

A technology cannot be transferred unless it exists. When the 1972 act gave NHLBI responsibilities which, a few years later, would coalesce under the formal rubric of "technology transfer," the technologies that were ripe for transfer were technologies in cardiovascular diseases and to a much lesser extent in pulmonary and blood diseases. In the initial program plan following the 1972 act, the following five areas were to be given special emphasis (72):

- prevention of heart attacks—the greatest killer in our nation;
- high blood pressure education—millions of our citizens do not know that they have high blood pressure, that it may lead to serious complications such as stroke and death, and that treatment is available;
- expansion of the attack on lung diseases—a heretofore neglected area;
- development of a national blood policy—a critical national need;
- methods of controlling sickle cell disease.

Thus, the primary emphasis in the lung and blood areas had to be on knowledge development, while knowledge application was a more immediate reality for cardiovascular diseases. Furthermore, the two cardiovascular objectives were linked; hypertension is a major risk factor for heart failure and coronary disease, as well as for strokes.

NHLBI's support of clinical trials generally reflects the situation where knowledge application is a more immediate reality for cardiovascular diseases than for lung and blood diseases. Appendix C summarizes NHLBI's recently com-

pleted, current, and planned clinical trials. Three of these trials will be described shortly.

The demonstration activities in prevention, education, and control also have a heavy cardiovascular emphasis. These activities are initiated and/or implemented by the Office of Prevention, Education, and Control (OPEC) or by the operating divisions. OPEC's recent activities have included:

- the National High Blood Pressure Education Program, involving State and Federal agencies and over 150 private organizations;
- the Foods for Health project, a joint collaborative effort with Giant Foods, that is now serving as the basis for a number of nutrition education programs;
- the Blue Cross/Blue Shield demonstration effort to stimulate high blood pressure programs at the worksite (Blue Cross/Blue Shield has developed a nationwide marketing program in this area following the demonstration project);
- the High Blood Pressure TV Module, an alternative to the Public Service Announcement for conveying educational messages via TV;
- the Quit Smoking Community Intervention Program, which uses a series of TV smoking cessation segments coupled with local American Lung Association promotion and materials; and
- the Health Professionals Awareness of High Blood Pressure Media Messages, a survey of whether health messages in the lay media are absorbed by health professionals, to determine whether the lay media might be an alternative means (e.g., compared to professional journals) of reaching the medical profession.

Examples of demonstration activities under the operating divisions are the grant-supported community intervention programs and the contract-supported workplace intervention programs of the Division of Heart and Cardiovascular Diseases. The three community intervention programs—the Stanford, Minn., and Pawtucket, R.I. Heart Disease Prevention Programs—are attempting to demonstrate that a widespread community education and risk reduction effort will result in lowering cardiovascular risk factors that, in turn, will result in decreased cardiovascular mortality. The three workplace intervention programs—through the University of Maryland, Ford Motor Co., and Westinghouse Corp.—are evaluating the impact of high blood pressure control in the workplace.

As noted in the introduction to this chapter, age-adjusted cardiovascular disease death rates have fallen 25 percent in the decade between 1968 and 1978, compared to a 10-percent decline in age-adjusted death rates from noncardiovascular causes (see fig. 8). The rate of decrease also accelerated in 1973, and now there is a 3-percent annual reduction in deaths due to coronary heart disease and a 5-percent reduction in deaths due to strokes (105).

In 1972, NHLBI initiated two large programs. One was the National High Blood Pressure Education Program. The other was the Hypertension Detection and Followup Program.

The National High Blood Pressure Education Program, coordinated and staffed by NHLBI, involves State and Federal agencies and over 150 private organizations (36). Surveys on public knowledge about high-blood pressure conducted in 1973 and in 1979 showed the following changes. First, the belief that hypertension is a serious condition increased from 63 percent in the 1973 survey to 73 percent in 1979. Second, 83 percent of those surveyed in 1979 had had their blood pressure measured within the past year, compared to 73 percent in the 1973 survey. Third, about twice as many people knew in 1979 what a normal blood pressure was. Fourth, 40 percent more people understood that hypertension did not have reliable symptoms. And fifth, in the 1979 survey, more people knew that effective treatment was available, and more were also following their prescribed therapies (78).

The Hypertension Detection and Followup Program was a community-based randomized controlled trial involving 10,940 persons with high-blood pressure, comparing the effects on 5-year mortality of a systematic antihypertensive treatment program (stepped care, or SC)

and referral to community medical therapy (referred care, or RC). Stepped care patients were offered therapy in special centers, and therapy was increased stepwise to achieve and monitor reduction of blood pressure to or below set goals. Referred care patients were referred to their usual sources of care, with special referral efforts for those with more severe hypertension or organ system damage. Patients were apportioned among three diastolic blood pressure (DBP) strata (subclassified by age, sex, and race) on entry into the study: 90 to 104, 105 to 114, and 115 or greater mm Hg.

The study was designed to answer the questions which were unresolved by previous studies conducted within the Veterans' Administration's medical care system:

1. Is a systematic approach to antihypertensive therapy (stepped care) compared to community care effective in reducing risk of 5-year mortality for all hypertensive adults in the community?
2. Can a substantial proportion of all hypertensives, detected in general populations, be brought under pharmacologic management aimed at reducing blood pressure to normotensive levels and kept under such management?
3. Do the benefits of therapy exceed severe toxicity in the stratum with mild hypertension, as well as in the more severe hypertensive strata?
4. Is antihypertensive therapy effective in young adults and in women and equally effective in blacks and whites?
5. Can morbidity and mortality from coronary artery disease be decreased by antihypertensive therapy?

The results of the clinical trial were as follows (34,35):

1. Over the 5 years, 50 to 65 percent of SC patients were at or below the goal DBP, compared to 30 to 44 percent in the RC group.
2. Five-year mortality from all causes was 17 percent lower for the SC group compared to the RC group, and 20 percent lower for the SC subgroup with the lowest entry DBP of 90 to 104 mm Hg. The latter finding is particularly significant, because about 70 percent of all hypertensives are in the lower DBP stratum, and approximately 60 percent of mortality attributable to high blood pressure occurs in people with this DBP range.
3. The 5-year stroke incidence was significantly less in the SC group (1.9 per 100 persons) than in the RC group (2.9 per 100 persons).
4. The death rate from strokes in the SC group (1.06 per 1,000 persons vs. 1.91 per 1,000 persons for the RC group) indicated that the stroke death rate decreased to near the level of stroke death rate in the general U.S. population (0.83 per 1,000 persons).
5. The SC group's reduction in mortality and morbidity from strokes occurred in all subsets: a) 45-percent reduction for those with entry DBP of 115 mm Hg or greater; b) 30-percent reduction in incidence among white women and decreased incidence in all subgroups; c) 27-percent reduction even in the youngest participants (ages 30 to 49 years at entry); and d) 45-percent reduction in incidence among the oldest participants (ages 60 to 69 years at entry).

Thus, this large clinical trial, with total costs approaching $70 million, showed more intensive care with available therapies could lead to a significant decrease in mortality and morbidity from hypertension and that these benefits were found in treating "mild" hypertensives as well.

The results of this study were first published in the *Journal of the American Medical Association* in December 1979 (34). In a sampling of physicians collected to see how timely dissemination of new medical information reached the practicing physician, 40 percent of family physicians were aware of the study within 2 months of publication, and 63 percent of internists learned of it within 6 months. Of the 40 percent of family physicians aware of the study, 98 percent were able to correctly answer questions about the reduction in mortality and the benefits of treating mild hypertension. Eighty percent of the family physicians and 50 percent of the internists learned of the study from medical journals, and 40 percent of the internists learned of it from

continuing medical education courses (the remaining percentages learned of the study from colleagues or the lay press) (110).

In sum, as a result of these activities, the public is much more aware of hypertension as a disease with serious but preventable consequences, new information on the effectiveness of treating even "mild" hypertension has been generated, and this information has disseminated rapidly to the medical community.

In 1975, the Aspirin Myocardial Infarction Study (AMIS) was initiated to test whether the regular administration of aspirin to men and women who had experienced at least one documented myocardial infarction (heart attack) would result in a significant decrease in mortality over a 3-year period. Secondary objectives were to evaluate the effects of aspirin on the incidence of coronary heart disease mortality, coronary incidence (defined as coronary heart disease mortality or definite, nonfatal myocardial infarcion), and the incidence of fatal or nonfatal stroke.

Previous studies had suggested the possibility that aspirin use might lead to these effects, and together with the antiplatelet properties of aspirin, led to NHLBI's study.

The AMIS study included 4,524 persons between the ages of 30 and 69, randomized over a 13-month period to either 1 gram of aspirin (approximately three aspirin tablets) per day (2,267 persons) or to a placebo (2,257 persons) and followed for 3 years. After the random allocation, however, a difference ($p < 0.05$) was found between the two groups in the baseline distribution of seven characteristics such that the aspirin group had significantly higher percentages of patients with heart failure, angina pectoris, ECG-documented arrhythmias, and use of digitalis, nitroglycerin or long-acting nitrates, propranolol (or other beta-blockers), and "other drugs."

The results were as follows:

1. Total mortality during the entire followup period was 10.8 percent for the aspirin group and 9.7 percent for the placebo group. Adjusted for 15 baseline variables, including the seven for which the aspirin group had significantly higher percentages, total mortality was 10.5 percent and 10.0 percent, respectively.
2. Three-year mortality was 9.6 percent for the aspirin group and 8.8 percent for the placebo group.
3. Definite nonfatal myocardial infarction occurred in 6.3 percent of the aspirin group and 8.1 percent of the placebo group.
4. Coronary incidence (coronary heart disease mortality or definite nonfatal myocardial infarction) was 14.1 percent in the aspirin group and 14.8 percent in the placebo group.
5. Symptoms suggestive of peptic ulcer, gastritis, or erosion of the gastric mucosa occurred in 23.7 percent of the aspirin group and 14.9 percent of the placebo group.

The investigators reached the following conclusions (2):

> The studies that have been cited found trends in mortality favorable to aspirin. However, in none of these studies were the differences between aspirin and placebo unequivocally statistically significant when all enrolled patients were included in the analysis . . . The fact remains that in terms of the primary endpoint, AMIS found no benefit from aspirin. This trial is the largest completed and published investigation of aspirin in the post-MI population, and more weight must be given to its results. These results indicate that aspirin perhaps is helpful in reducing the frequency of non-fatal MI but leads to an increased incidence of side effects. They clearly indicate that the regular administration of aspirin in this dose does not reduce three-year mortality in patients with a history of MI. In summation, based on AMIS results, aspirin is not recommended for routine use in patients who have survived an MI.

Soon after publication of this clinical trial, it and five others (including two other newly published trials)—which had a total of over 10,000 myocardial infarction patients randomized between aspirin and double-blind placebo controls and in which over 1,000 patients died—were reviewed by the Society for Clinical Trials. The consensus that emerged was that aspirin did reduce the risk of death, but that the smallness of

the reduction was what had led to difficulties in interpretation even in the largest trials. It was estimated that, across all six trials, the overall reduction in the odds of reinfarction was 21 percent (standard error ± 5 percent) and that some 70-odd deaths had been prevented (39).

Recently, NHLBI and NCI have initiated a clinical trial to test the preventive efforts of both aspirin (for cardiovascular mortality) and beta carotene or vitamin A (for cancer incidence). The study is a double-blind randomized placebo trial involving 21,500 healthy U.S. male physicians with initial ages of 50 to 75 years.

Policy analysts, preparing for the first renewal of the 1972 act, asked these questions in 1975 (109):

> Is there really anything new, in 1975, about coronary by-pass except the number of such operations performed? And has the coronary bypass procedure by now been shown to lengthen lives; or does it still mainly reduce pain symptoms of angina pectoris?

With an average cost of about $15,000 and up to 100,000 coronary bypass procedures performed annually in the United States (including celebrity patients such as Secretary of State Alexander Haig and, more recently, past Secretary of State Henry Kissinger), the questions being asked today are basically the same as those in 1975, with the exception of being more focused. For example, in what types of coronary artery disease can bypass surgery improve mortality? And is reducing symptoms a proper use of this technique? These and related questions are still being addressed in NHLBI's Coronary Artery Surgery Study, initiated in 1973 with a goal of 800 randomized patients to be followed for at least 4 years, and including a registry of 25,000 patients referred for coronary arteriography.

Related to this surgical therapy is the relatively new technique of percutaneous transluminal coronary angioplasty (PTCA), in which a special catheter with a tiny balloon at its tip is inserted in an arm or leg artery and passed up into the narrowed coronary artery, where the balloon is inflated to press the atherosclerotic plaque against the vessel wall to enlarge the narrowed area. The first angioplasty in a peripheral artery was performed by Dotter and Judkins in 1964, and the first coronary artery procedure was done in 1977 by Grüntzig.

NHLBI sponsored a workshop in June 1981 for investigators active in this field, and of the 205 procedures reported at the workshop, 116 were considered successful. The technique may be applicable to no more than 5 percent of patients undergoing coronary bypass surgery at the present time and is still considered experimental. NHLBI maintains a registry, and by early 1982, had over 80 centers in the United States, Canada, and Europe reporting a cumulative total of 3,066 patients (74).

These selected examples show both the extent and limitations of NHLBI's influence on the transfer of technologies under its purview. In the case of hypertension control, both established and new applications are converging to produce not only heightened awareness of the problem among the public and health professionals, but also significant effects on cardiovascular-related morbidity and mortality. In the case of aspirin use for preventing heart attacks, chance fluctuations in the risk factors of the aspirin v. control groups of the NHLBI-sponsored clinical trial led at least one group of reviewers to conclude that the trial mistakenly indicated no benefit. The momentum of coronary bypass surgery—reflected in the large numbers of procedures currently being performed—appears to have gone far beyond the bounds of accepted indications. Whether the NHLBI clinical trial can cause the medical community to temper its enthusiasm for this procedure remains to be seen. Finally, in the emergence of PTCA, NHLBI's establishment of a registry is an example of its monitoring of emerging technologies and its attempt to steer this new technology along a rational path of development and dissemination.

The implications of these clinical trials and demonstration programs and the technology transfer process adopted by NHLBI are summarized in the following section.

CONCLUSIONS

Under the National Heart, Blood Vessel, Lung, and Blood Act of 1972, NHLBI operates under an explicit mandate to help transfer the results of research in these areas to the public and health professionals. The 1972 act specified the kinds of technology transfer activities to be conducted and the minimal administrative approach which was to be adopted. Among the responsibilities specified in the 1972 act were "programs for field studies and large-scale testing, evaluation, and demonstration of approaches to these diseases" and "public and professional education in these diseases." Health Information Programs were to provide the public and health professionals with information on these diseases, with special emphasis "to be placed upon disseminating information regarding diet, exercise, stress, hypertension, cigarette smoking, weight control, and other factors related to prevention." Prevention and control programs were to be established with other governmental and private health agencies, and national research and demonstration centers were to be established in these diseases.

In the intervening decade since the 1972 act, the context in which these transfer activities take place has expanded to include economic, legal, social, and ethical issues in addition to the traditional scientific issues of safety and effectiveness. These added emphases have led to organized efforts in the NIH Director's Office (i.e., OMAR activities), and within the Public Health Service (i.e., the now defunct NCHCT and its administrative successors). These broadened interests in technology transfer in turn have led to a parallel broadening of the objectives of NHLBI's monitoring of technology transfer activities.

The 1972 act provided direction to NHLBI in technology transfer through the specific mandates to perform large-scale clinical trials and to initiate demonstration programs in prevention, education, and control. When the NIH Director's Office established a formal technology transfer focal point in 1978 through OMAR, NHLBI organized its MAP under a coordinator in the insititute's Office of Program Planning and Evaluation in the same year. These internal MAP activities have consisted primarily of monitoring technology transfer activities as formulated by the component groups within NHLBI. MAP has been used for coordinating activities of groups within and outside of NHLBI and for summarizing the institute's activities, as reflected, for example, in the technology transfer format used in preparing the NHLBI Director's annual reports. And until the current, ongoing revision of MAP, NHLBI's "medical application accomplishments have not been synthesized into a single document, nor has there been a NHLBI focus to track and facilitate developing, assessing, validating, and transferring medical applications. The MAP plan provides a mechanism for routinely documenting activities and accomplishments and for the periodic evaluation of the NHLBI MAP" (75).

The current objectives of MAP are: 1) to serve as a source for an inventory and status information on all high-priority technologies in transition; 2) to coordinate activities within NHLBI and between NHLBI and other portions of NIH or external agencies; 3) to provide visibility to NHLBI's transfer activities and their accomplishments; 4) to maintain an awareness of the state-of-the-science of technology transfer methods; and 5) to ensure that MAP is incorporated into NHLBI's planning process (75). Past efforts have concentrated on objectives 2 through 4. The new emphases are on objective 1, the inclusion of new and established technologies in transition in addition to an emerging technologies list, as well as more precise criteria for identifying these technologies; and on objective 5, incorporating MAP into NHLBI's planning process. These objectives are to be linked by integrating the identification and tracking of technologies in transition into the NHLBI Implementation Planning Process.

This linkage raises the familiar issue of whether emphasizing targeted research and clinical application comes at the expense of basic research, especially at a time of restricted funds. At the time of the 1972 act, these concerns were barely raised (109), especially since the transfer

reponsibilities were accompanied by increased funds. And, as already discussed, NHLBI implemented the legislated programs as additions to its basic research mission and passively monitored these activities. Currently, NHLBI emphasizes that technologies identified through any systematic process will originate with the divisions and branches and their advisory groups. The use of program advisory committees is seen as a method of identifying technologies that have reached an appropriate state of development and represent significant needs. Thus, targeted v. basic research is not a crucial issue.

On the other hand, downplaying a formal system of assessment at the Public Health Service level may filter down to the NHLBI effort, with the result that MAP's purpose remains to monitor and summarize technology transfer activities instead of being expanded to include it in the institute's program planning. This effect may be minimal as long as NHLBI concentrates on efficacy and safety criteria in its transfer functions, as this role would be consistent with its basic mission.

There are three other issues of importance for NHLBI's technology transfer activities. First, the formalization of NHLBI's MAP mirrors closely the development of technology transfer activities at the levels of the NIH Director's Office and of the Public Health Service. With the demise of NCHCT, a focal point for the extrascientific (i.e., economic, legal, social, and ethical) issues outside of NIH has been lost. But the impact of NHLBI's activities may be minimal, as there still exists OMAR in the NIH Director's Office to partially insulate NHLBI from being directly involved in these extrascientific issues.

Second, even if NHLBI continues to try to formalize MAP and integrate it into the institute's program plans, this activity may be relatively low on the institute's list of priorities. In a period of fiscal retrenchment, competition for funds within NHLBI will increase, and MAP may again revert to its monitoring and summarizing role.

Third, fiscal retrenchment would directly affect NHLBI's technology transfer activities. The medical community regards the large-scale clinical trial as a critical activity in the biomedical research spectrum and indispensable for determining the efficacy of treatment or preventive regimens (11,42). But the flow of technology does not simply proceed in one direction and along one path from basic research to clinical application. The Aspirin Myocardial Infarction Study and the Coronary Artery Surgery Study represent assessments of technologies already in use—the first to test a new indication for an old medicine, and the second to help clarify use of a surgical technique which is valid but costly. These evaluations of existing technologies, although a proper use of NHLBI's clinical trials program, compete with evaluations of emerging technologies for funding.

The research base in areas not yet ripe for transfer in the past decade—lung and blood diseases and selected areas of cardiovascular disease—is beginning to produce results. There will therefore be more emerging technologies to evaluate through clinical trials while the interest in reevaluating existing technologies is maintained. As long as NHLBI continues as the principal U.S. source of large-scale clinical trial support for these diseases, demands on this crucial link between research and clinical application, and the underlying competition between evaluations of emerging v. existing technologies, will increase.

A more immediate effect of fiscal restraints would be in NHLBI's demonstration programs. For example, the National High Blood Pressure Education Program was initiated in 1972. Ten years later, it is still funded through NHLBI. The only way in which new demonstration programs can occur is through additional funds or through termination or transfer of existing demonstration programs to other organizations. But demonstration programs often involve the "public goods" issue; i.e., the majority agree that these programs are needed, but no other organization wants to assume responsibility or has the funds to do so.

Thus, fiscal restraints may have the effect of retrenchment both in the management of technology transfer and in the specific activities which comprise the technology transfer process.

Chapter 8

Findings and Conclusions

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Chapter 8

Findings and Conclusions

This technical memorandum has described and examined the role of the National Institutes of Health (NIH) in the transfer of technologies to the health care system. Because it is a technical memorandum and not a full OTA report, it does not present recommendations or policy options for congressional consideration.

The major finding of this study is that, despite some problems relating to the timely transfer of potentially helpful technologies, the major weaknesses of the present process for technology transfer are: 1) inadequate attention as to whether technologies being considered for transfer rest on sufficient knowledge to justify such transfer, and 2) insufficient attention to the scientific evaluation of emerging technologies to determine their potential benefits, risks, costs, and conditions for appropriate use.

Very importantly, the above finding is a general criticism of the current process of medical technology transfer. NIH is only one of the actors, although it is a crucial and influential one. And it should be noted that NIH is responsible for much of the evaluation that does take place and for a great deal of the basic science knowledge that now exists.

It is also important to realize that "NIH" is not a single, tightly structured entity. It is a loosely coordinated collection of semiautonomous organizations—each pursuing related but individual goals, facing different research and public responsibilities, and under varying types and amounts of external pressures.

Policies toward technology transfer must try to satisfy a complex mixture of objectives; they must blend a concern with basic science research directed toward eventual application with a concern for science for more immediate practical purposes. Ultimately, these two concerns may merge—the knowledge may lead to applications in health care or even in some other field. Decisions must be made in the present, but they must take into account both immediate and long-term implications.

OTA finds that five goals should underlie policies and activities of technology transfer: 1) the identification of areas where the knowledge base is inadequate to produce effective technologies, and the setting of priorities among such areas; 2) the support and encouragement of basic and applied research in areas of inadequacy; 3) the generation of adequate knowledge about the readiness for transfer of technologies under development; 4) the creation of efficient mechanisms to demonstrate and then transfer technologies judged to be ready for use; and 5) the creation of mechanisms to monitor the actual use and effects of technologies in the health care system. Further, each of these five goals must be supported by a comprehensive and readily accessible source of information collection and dissemination.

As these five goals indicate, the transfer of technology is not in itself always a good thing nor always a bad thing. Unfortunately, however, organizations and individuals very often divide into two factions: those who believe that medical technologies should be transferred as quickly as possible, and those who believe that the rate of transfer is too rapid already. Such a generalized position is not helpful. The approach should be to examine each technology, class of technologies, or disease area and ask what is known about any technology being considered for transfer or about the knowledge base being urged for development into technologies.

FINDINGS RELATED TO THE ASSESSMENT OF MEDICAL TECHNOLOGIES

NIH's principal formal activities in the evaluation of medical technologies are its clinical trials and its consensus development conferences. It is by far the most important supporter of these types of activities. With the disappearance of the National Center for Health Care Technology (NCHCT), it remains as the only major focus for such activities.

The arguments in favor of or against NIH's involvement in evaluating medical technology are still the same as they were before NCHCT's demise. The reasons that argue in favor of its playing a large, perhaps expanded, role are:

- It has relatively greater fiscal and personnel resources at its disposal than do other agencies.
- It has strong ties to the academic medical centers.
- It has a good reputation among practicing physicians.
- It has a much higher than average institutional ability to accomplish objectives.
- It has experience in assessing medical technologies, especially their efficacy and safety.

The reasons for NIH's not becoming more involved with technology assessment activities are:

- Evaluation can be expensive in terms of time, attention, personnel, and, especially, funds. With a constrained budget, assessment directs resources away from the research mission of NIH.
- NIH's primary orientation is as a developer of knowledge and technologies, not as a "gatekeeper" or a critical evaluator of technology.
- Its personnel are more appropriate for its research mission than for technology evaluation. For example, the agency has an inadequate number of assessment methodologists, epidemiologists, and health services professionals for an expanded role in assessment activities.
- Th agency has a large enough and difficult enough task as it is, without the enlargement and formalization of the complicated function of evaluation.

Nevertheless, OTA finds that the evaluation function is so critical to the successful transfer of appropriate technologies that NIH should approach assessment in a more visible and structured manner and should strongly consider expanding its assessment activities. Funding and carrying out clinical trials, for example, is a function already supported by NIH. This function is consistent with the scientific orientation of NIH. Synthesizing available information on a particular technology, especially that concerning efficacy and safety, also seems appropriate for a scientific institution. On the other hand, considering broader implications of technology use, such as socioethical and economic factors, and arriving at policy judgments such as whether a specific technology should be covered in the medicare program may be better done by those more familiar with clinical medical practice and with policies toward technology use. This function might be better assigned to another part of the government.

The National Heart, Lung, and Blood Institute (NHLBI) is an example of an institute where the assessment and transfer function has been given much thought, where formal and effective processes have been developed, and where the attention given to such activities seems to be paying off in terms of successful diffusion of information and technologies.

The identification of emerging or existing technologies in need of assessment is a crucial aspect of technology transfer and assessment. NIH, through the Office for Medical Applications of Research (OMAR), was mandated to develop a yearly list of priority technologies for NCHCT. With NCHCT no longer in existence, it will be up to OMAR and NIH whether a list will be collected in the future. If that activity is discontinued, there will be no formal procedures in place, except in NHLBI, to identify technol-

ogies in need of assessment. Of particular importance is that NIH assure the evaluation of technologies whose development it has supported. Not only would such procedures be helpful because they could lead to needed evaluations, but the process of identification itself may pay dividends in terms of: 1) setting priorities for research, and 2) building a base of experience in thinking through the criteria by which a technology is judged as ready for transfer. At the same time, the process of identifying technologies must not be allowed to become overly burdensome to the institutes and research personnel.

The level of assessment will become even more critical in future years. Budget pressures will put even greater demands on each research dollar. This budget constraint, combined with an effort to stabilize the number of new competing grants awarded, is likely to influence negatively the number or size of future clinical trials.

FINDINGS RELATED TO THE TRANSFER OF MEDICAL TECHNOLOGIES

Only rarely does NIH actually transfer technologies. In fact, most of the Federal Government's "technology transfer" activities do not actually involve the transfer of technologies. More accurately, the vast majority of such activities are those which: 1) provide information about technologies, thus encouraging or discouraging their transfer, or 2) demonstrate in a few selected settings the potential uses of new technologies.

In the first type of activity, the Government is not involved in the provision of actual medical technologies at all. Instead, it is generating, analyzing, or disseminating information. For example, publication of the results of applied research or of clinical trials may affect the transfer of technologies in question.

With the second type of activity, funds and technical consultation may be provided to support the testing of the performance, acceptance, etc., of new technologies. Thus, some transfer of technology takes place, but the extent is usually small and the conditions of use are relatively controlled.

At NIH, the institutes that have legislative mandates to conduct technology transfer activities, especially in the form of demonstration and control programs, do more of it than do institutes without such mandates. The National Cancer Institute (NCI), NHLBI, and the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) are the clearest examples of this. Thus, it is possible that if Congress wished to increase this form of activity it could do so by extending the mandate to other institutes.

The area of control programs often brings NIH into the fuzzy interface between biomedical research and health care delivery. Under most circumstances, this type of activity bears careful watching so that NIH is not *unintentionally* brought too far into the delivery aspect of health care. In certain instances, it is imperative that the agency *not* get too deeply involved in demonstration and control programs that verge on health care delivery. That can occur when the knowledge base is inadequate for the development of effective and safe technologies. *Efforts to transfer technologies prematurely are especially harmful when such transfer is not only to academic health centers (where conditions may be more controlled) but also into community hospitals and other medical practice sites.* One of these instances may be in the process of occurring if the critics who believe that NCI is moving too rapidly in its transfer of certain technologies, primarily through its demonstration and control programs, are correct. OTA did not have the mandate to study that specific example; therefore further research may demonstrate otherwise. The situation, however, is worth additional examination.

Note that OTA is not saying that NIH is doing an inadequate job of developing or keeping track of the state of basic science. *The finding is simply that in making decisions to support the*

demonstration and transfer of specific medical technologies, attention should always be given to the knowledge base on which those technologies rest. The basic and applied research base is not at an equal level of development and understanding across all areas of inquiry. Thus, the priority and funding given to technology evaluation becomes doubly important, for only through careful scientific evaluation of efficacy and safety (and at times of cost and social implications) can informed decisions be made about readiness for transfer and therefore about the appropriate use of demonstration and control programs.

The first type of activity mentioned above—generating and disseminating information—may not be as obviously seen as transfer supporting, but it is a crucial aspect of technology transfer and is actually a far more influential and a much larger activity than demonstration and control programs. (It should be noted, however, that in a very substantial sense, demonstration and control programs are in part also "information-related programs.")

The current effectiveness of information activities depends on the substance of the information and the process by which it is gathered and disseminated. OTA finds that *the process by which transfer-related information is disseminated appears to be excellent in most cases.* The National Library of Medicine and its MEDLARS system have played a key role in information dissemination. Similarly, NIH and its intramural and its funded researchers have made extensive use of opportunities for disseminating information through professional/scientific journals and other publications and through professional meetings.

The substance of the biomedical information generated is generally excellent, although, in keeping with above comments, more attention could be given to clinical trials and other assessment results.

In summary, NIH is one of the primary actors in the assessment and transfer of medical technologies. It is subject to a number of internal and external constraints and pressures, some of which urge it to be more active in transfer and some to be less active. OTA's conclusion is that a cautious approach, varying according to the specifics of each situation, would be more appropriate. NIH could devote more funds and attention to generating information on the potential benefits and risks of technologies, and then, when sufficient information exists, it could actively utilize its existing, adequate mechanisms to support appropriate transfer of medical technologies.

Appendixes

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APPENDIX A

Glossary of Acronyms

ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration (PHS)
AHA	American Hospital Association
AMA	American Medical Association
CBA	cost-benefit analysis
CC	Clinical Center (NIH)
CCOP	Community Clinical Oncology Program (NCI)
CCPDS	Centralized Patient Data System (NCI)
CCRC	Clinical Cancer Research Center
CDC	Centers for Disease Control (PHS)
CEA	cost-effectiveness analysis
CEA/CBA	cost-effectiveness analysis/cost-benefit analysis (when referred to as a class of analytical techniques)
CEAP	Clinical Efficacy Assessment Project
CHOPS	Community Hospital Oncology Programs (NCI)
COP	Clinical Oncology Program (NCI)
CRC	Cancer Research Center
CTEP	Cancer Therapy Evaluation Program (NCI)
DCRT	Division of Computer Research and Technology (NIH)
DCT	Division of Cancer Treatment (NCI)
DHEW	Department of Health, Education, and Welfare (now DHHS)
DHHS	Department of Health and Human Services (formerly DHEW)
DOL	Department of Labor
DRCCA	Division of Resources, Centers, and Community Activities (NCI)
DRG	Division of Research Grants (NIH)
DRR	Division of Research Resources (NIH)
DRS	Division of Research Services (NIH)
ECOG	Eastern Cooperative Oncology Group (NCI)
ESRD	end-stage renal disease
FDA	Food and Drug Administration (PHS)
FIC	Fogarty International Center (NIH)
GAO	General Accounting Office (U.S. Congress)
HCFA	Health Care Financing Administration (DHHS)
HEW	Department of Health, Education, and Welfare (now DHHS)
HHS	Department of Health and Human Services (formerly DHEW)
HRA	Health Resources Administration (PHS)
HSA	Health Services Administration (PHS)
IATC	Interagency Technical Committee
IOM	Institute of Medicine (NAS)
I/RDs	institutes and research divisions (NIH)
IRG	initial review group
LCRC	Laboratory Cancer Research Center
MAP	Medical Applications Program (NHLBI)
MEDLARS	Medical Literature and Analysis Retrieval System (NLM)
MI	myocardial infarction
NAS	National Academy of Sciences
NCAB	National Cancer Advisory Board
NCHCT	National Center for Health Care Technology (OASH)
NCHS	National Center for Health Statistics (OASH)
NCHSR	National Center for Health Services Research (OASH)
NCI	National Cancer Institute (NIH)
NEI	National Eye Institute (NIH)
NHLBI	National Heart, Lung, and Blood Institute (NIH)
NHLI	National Heart and Lung Institute (now NHLBI)
NIA	National Institute on Aging (NIH)
NIAAA	National Institute on Alcohol Abuse and Alcoholism (ADAMHA)
NIADDK	National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIH)
NIAID	National Institute of Allergy and Infectious Diseases (NIH)
NIAMDD	National Institute of Arthritis, Metabolism, and Digestive Diseases (now NIADDK)
NICHD	National Institute of Child Health and Human Development (NIH)
NIDA	National Institute on Drug Abuse (ADAMHA)
NIDR	National Institute of Dental Research (NIH)
NIEHS	National Institute of Environmental Health Sciences (NIH)
NIGMS	National Institute of General Medical Sciences (NIH)
NIH	National Institutes of Health (PHS)
NIMH	National Institute of Mental Health (ADAMHA)

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NINCDS	National Institute of Neurological and Communicative Disorders and Stroke (NIH)
NLM	National Library of Medicine (NIH)
NSF	National Science Foundation
OASH	Office of the Assistant Secretary for Health (DHHS)
OHRST	Office of Health Research, Statistics and Technology (OASH)
OMAR	Office for Medical Applications of Research (NIH)
OSHA	Occupational Safety and Health Administration (DOL)
OTA	Office of Technology Assessment (U.S. Congress)
PHS	Public Health Service (DHHS)
PTCA	percutaneous transluminal coronary angioplasty
R&D	research and development
RCT	randomized clinical trial
RFA	request for applications
RMP	Regional Medical Program
SAQC	Statistical Analysis and Quality Center (NCI)
SEER	Surveillance, Epidemiology, and End Results program (NCI)
SSA	Social Security Administration (DHHS)
VA	Veterans Administration

Appendix B

Background Materials: Grants, Contracts, and Peer Review

The funding mechanisms of the extramural programs of the National Institutes of Health (NIH) have an impact on the various technology transfer activities. In large part, this impact is due to the way in which the extramural projects are selected and administered. This appendix describes the awarding process for grants and contracts, the two primary funding mechanisms. In addition, it presents a review of recent studies of the peer review system and a discussion of various grant mechanisms.

Research Grants

The main types of research grants are research project grants, program project grants, and center grants. According to the NIH publication *NIH Extramural Programs* (52), they may be distinguished as follows:

- Research project grants are awarded to an institution on behalf of a principal investigator to facilitate pursuit of a single scientific focus or objective in the area of an investigator's interest and competence. Institutional sponsorship assures the NIH that the institution will provide facilities necessary to accomplish the research and will be accountable for the grant funds. A research grant may occasionally be awarded directly to an individual who has access to adequate facilities and resources for conducting the research.
- Program project grants are awarded to an institution on behalf of a principal investigator for the support of a broadly based, often multidisciplinary, long term research program with a particular major objective or theme. A program project involves the organized efforts of groups of investigators who conduct research projects related to the overall program objective. The grant can provide support for the projects and for certain shared resources needed for the total research effort. Each project supported under a program project grant is expected to contribute to the overall program objective.
- Center grants, awarded to institutions on behalf of a program director and a group of collaborating investigators, provide support for long term, multidisciplinary programs of research and development. The distinction between program project and center grants is that center grants are more likely to have a clinical orientation and are usually developed in response to announcements of the specific needs and requirements of [an institute or division]. Center grants support programs in critical health problem areas including: research and development; demonstration of advanced techniques for the diagnosis, treatment, prevention, or control of disease; education; and other related nonresearch components. Although center grants may support both the projects and the "core" or shared resources, in some instances, only "core" costs are provided under the center grant, and project support must be requested through the project or program project mechanisms.

Research grants may be used to pay the salaries of personnel, the purchase of equipment and supplies, travel, publication, the institution's direct costs, and other purposes directly associable with the research. The award also includes reimbursement for indirect costs, or overhead, to the investigator's institution. Establishing an overhead rate that is equitable to both the government and the institution continues to be a problem (114).

Grant applications submitted to NIH are received centrally in the Division of Research Grants (DRG). This Division, one of the research and support divisions at NIH, has most of the responsibility for administering the grants applications review program, although each institute's participation in the process is essential with respect to grants awarded out of its individual appropriation. DRG collects, stores, analyzes, evaluates, and retrieves management and program data needed in the administration of these programs. It also provides advisory and consultative services to grantees relating to grant policy and management matters.

The most important function of DRG, though, is to screen all incoming grants applications, determine the relevance of each application to the overall mission of NIH, and assign acceptable applications to an appropriate initial review group (IRG, or more commonly "study section") for scientific peer review and to an appropriate institute for funding review. The two reviews, referred to as the "dual review system," occur sequentially. DRG does not assign the applications for review arbitrarily. Instead, assignment to an IRG is based on the match between the subject of a proposed research project and the review responsibilities and scientific expertise of the IRG's members; assignment to an institute is based on the institute's legislatively mandated program responsibility. Ap-

plications may be assigned to two institutes at once if the subject matter is pertinent to the program responsibilities of both. Should the primary institute decide not to provide funding, the other institute may consider it.

Depending on the type of research proposed, the first level of scientific and technical merit review is by an IRG located either within DRG or within an institute. IRGs within DRG are called study sections. Currently, there are four groups of study sections—Behavioral and Neurosciences Review, Biomedical Sciences Review, Clinical Sciences Review, and Special Review—which contain 55 review groups representing at least 50 disciplines. IRGs in the institutes are usually multidisciplinary and are constituted to review more complex program project and center grant applications.

The IRGs are composed of 10 to 15 highly qualified nongovernment consultants selected on the basis of their recognized competence and achievements in their respective research fields. An NIH health scientist administrator serves as executive secretary of each group. The executive secretary reads each application and assigns it to two or more members of the IRG best qualified to judge the application in detail. When assessing the scientific and technical merit of an application assigned to their IRG, the members consider several factors, including: the training, experience, and research competence or promise of the investigators; the adequacy of the experimental design; the suitability of the facilities; and the appropriateness of the requested budget to the work proposed.

IRG members, who serve up to 4 years per appointment, meet three times a year to review applications. At the meetings, the applications are recommended either for approval, disapproval, or deferral for more information (which may be obtained using outside assistance or site visits) by majority vote. In addition, for applications recommended for approval, each member of the IRG individually and privately assigns a numerical rating that reflects a personal evaluation of the scientific merit of the proposed project. The executive secretary then combines these ratings into one priority score and prepares a written summary of the considerations, including a project description and critique, a recommended budget, an explanation of the IRG's recommendation, and notations about any special points. Both the priority scores and the summaries are then forwarded to the appropriate institutes and other awarding units for the second level of review.

Each of the awarding units has a national advisory council or an equivalent unit that reviews and determines approval of grant applications before a grant can be awarded. These councils are mandated by law, and some have minimum levels placed both on the number of times they must meet each year and on the number of members they must have. Members include authorities in scientific and health fields directly related to the program interests of the institute or division, as well as lay people noted for their interest or activity in national health problems. Except for the National Cancer Advisory Board (NCAB) and the National Library of Medicine Board of Regents, the council members are selected by the Secretary of Health and Human Services and serve 4-year terms.

The councils review grant applications in a broader context than the IRGs, because their recommendations are based not only on the IRG scientific and technical merit evaluations, but also on the needs of NIH and the missions of the individual institutes, the need for initiation of research in new areas, the degree of relevance of the proposed research to the missions of the institutes, and other policy issues. The council recommendations are forwarded to the institute director for funding. The priority scores assigned to the grant applications by the IRGs serve as a virtually inviolable guide to the advisory councils and to the awarding units in their decisions regarding the order in which the approved grant applications will be funded. However, while the councils can not change the priority scores, they can recommend that an approved application be classified to be funded or not to be funded based on program relevance. The projects approved by the councils are usually chosen according to rank until the budget is obligated. An approved grant application is not assured of funding, because there are almost always more eligible applications than available funds. A disapproved application, though, can not be funded.

R&D Contracts

The NIH publication *NIH Extramural Programs* (52) states that research and development (R&D) contracts:

> . . . are awarded to nonprofit and commercial organizations to foster and direct scientific inquiry toward particular new areas of research and development and to utilize advances in knowledge and technology to search for solutions to specific questions. Contracts are conducted with close NIH direction and monitoring; negotiations afford the contracting parties flexibility in establishing the details of their relationship at the outset of the contract work.

The same publication describes several types of R&D contracts: 1) research contracts focus on a specific research problem that has been identified by an

NIH component and requires central direction, control, and management, such as clinical trials of new and existing therapies; 2) development contracts are awarded for projects to produce substances, devices, systems, or other approaches to diagnose, prevent, treat, or control diseases; and 3) demonstration contracts are awarded when NIH desires to direct, or at least control closely, opportunities to demonstrate the feasibility of applying new advances to individual or community situations to solve certain health problems, such as cancer control programs. Contracts may also be awarded for certain types of research support services or resources (e.g., data processing, collection and distribution of materials needed to conduct R&D) as well as for conferences and workshops to facilitate scientific communication and evaluation.

The contract mechanism offers more universal competitive opportunities to all types of scientific sources. It is used by the Government to fulfill its specific program objectives. Thus, because the areas of work to be undertaken are already defined, offerors can compete for a commonly understood objective, and contract proposals received are evaluated within the framework of criteria announced to all competing sources.

Each awarding unit (institute or division) has developed slightly different methods to satisfy its research needs. The basic mechanism used to develop requests for proposals, to review contract applications, and to evaluate the progress and outcomes of contract products, though, are similar enough to be summarized in a general description. The scientific staff members within a given institute, with assistance from standing committees or ad hoc advisory groups, develop a research project description and plan. The concept of the project is then evaluated by a scientific review group composed largely of non-Federal advisors, in compliance with the law that mandates peer review for NIH contract projects. Next, the proposed project is released as a request for proposal (RFP), which specifies the terms, conditions, and provisions for the requested contract. The RFP appears in several appropriate publications, including the *Commerce Business Daily* and the *NIH Guide for Grants and Contracts*.

Contract proposals, submitted in response to an RFP, undergo several stages of review. First, they are reviewed by the institute's contracting officer and then by a scientific review group consisting mainly of nongovernment scientists with expertise in the relevant area. Their recommendations are sent to a contract review committee composed of senior program staff from the funding institute. During this review, the various elements of the proposals involving costs are examined by Government cost analysts in conjunction with technical personnel. Applicants determined to be in the "competitive range" have an opportunity to further defend or clarify their proposals in written or oral discussion with the contracting officer or senior program staff. Once the applicants have made their "best and final" offer, the remaining applications are reevaluated via further negotiations in order to determine the one to be funded. The ultimate objective of such negotiations is to reach a balanced equitable agreement. Occasionally, unsolicited contract proposals are received by DRG. They are forwarded to an appropriate institute, and if relevant to the institute's needs, are reviewed in a process similar to that for solicited proposals.

Once awarded, the progress and products of contract research are under the supervision and review of the contracting officer at the funding unit. Informal and formal procedures are used to monitor the performance of the contract project. A major difference between contract research and grant (and intramural) research, at least in theory, is that contractors are required to provide an end product based on specifications established by the institute before the research begins. With grant-supported and intramural research, requirements for production of a given outcome are generally much looser. Another difference between the funding mechanisms is that advisory councils or boards are not required to approve contract awards as they are mandated to do for grants. Nevertheless, they are usually quite involved in the awarding unit's research planning process, which includes the allocation of resources for both grants and contracts.

Recent Studies of the Peer Review System

The peer review mechanism, being at the heart of the grant-in-aid award system, has been the subject of a number of recent studies. The General Accounting Office (GAO) (27) compared the operation of the peer review and progress monitoring systems at NIH and the National Science Foundation (NSF). In general, GAO found the NIH procedures better. However, GAO's concern was not, as they stated, with the quality of the review or the fairness of the review, but with the process of the review. Examining the quality of the scientific review is a different problem and exceeded the resources available to GAO at the time.

NIH conducted a review of its own peer review system in the late 1970's (50,51). Perhaps, not unexpectedly, they found the system to do a good job. Recommendations on which action have been taken

were those directed at the mechanics of the system. "A few recommendations were made regarding substantive issues of peer review but action on these was deferred by the NIH Director pending further study" (27).

The President's Cancer Panel has announced that it will host discussions in various cities around the country during 18 months to begin early in 1982. The purpose of those meetings is to hear opinions about the submission and review of grant applications at the National Cancer Institute (NCI) (announcement of Dr. Armand Hammer at the NCAB meeting, Feb. 1, 1982).

NSF placed a contract with the National Academy of Sciences (NAS) for a study of their peer review system. Two reports from that study have been published. The first (15) appeared in *Scientific American*. It reported:

1. A high correlation between reviewer ratings and grants awarded.
2. Absence of a high correlation between grants awarded and previous scientific performance of the applicants. ("This result was unexpected.")
3. That reviewers from major institutions did not favor applications from other major institutions.
4. That length of the scientific career of the applicant had no strong effect on review ratings.
5. Low or moderate correlation between reviewer ratings and:
   - prestige rank of applicant's current academic department;
   - academic rank;
   - geographic location;
   - NSF funding history over last 5 years; and
   - place of Ph. D. training.

The second paper, published in *Science* (14) reported rather more alarming results. Seventy-five applications from three different NSF programs that had been reviewed by the NSF peer review system were subsequently reviewed by other groups of peers. Surprisingly (to some, at least) and dismayingly (to more, perhaps), the ratings bestowed on about 25 percent of the applications by the two review groups differed enough to have affected whether or not the application would have been funded. The disagreements went both ways. In some cases, the NSF peer reviewers' ratings that resulted in a decision to fund an application was reversed by the second group. In other cases, an NSF review rating that would have meant no funding was changed sufficiently that the second rating would have resulted in funding. The two review groups did not differ in scientific accomplishments or esteem, and both appeared to be equally "peer." The authors of the study concluded that the "luck of the draw" in reviewers has a significant impact on how an application fares.

The NSF peer review system typically uses some four or five scientists to review an application. The luck of the draw might seem more of a factor in that system than in an NIH study section with 15 scientists. The authors of the paper about NSF review reached no conclusion about the importance of the luck of the draw in the NIH system. However, it is the practice in NIH study sections to assign each application to a primary and a secondary reviewer. If those two reviewers differ from the other study section members, and the others have read the application less thoroughly, luck of the draw may be important. The probability that members read less carefully applications on which they are neither primary nor secondary reviewers is almost a certainty. Applications typically run to several score pages, and each study section considers an average of 80 to 100 applications at each of its three-times-a-year meetings.

One expert contacted by OTA in the course of writing chapter 6 of this report has served on both NIH and NSF review groups. He found the NIH system to be more thorough and that the active discussion of applications at study section meetings produced better reviews. He thinks that prejudice, favoritism, and ignorance of a subject show up in study section discussions and that this assures the applicants fairer consideration.

Some suggestions have been made to institute an appeals system for applicants whose rating is less than they think they deserve. Currently, the disappointed applicant must prepare another proposal. The time necessary to write a new application plus the time for another review (typically about 9 months from NIH's receipt of the application to a decision to fund or not to fund) means a long period with no decision. Furthermore if a preexisting grant expires before a new one is secured, part of the scientist's research program may have to be shut down.

An institute advisory board can suggest that an application be sent for a second review to a second study section. If the applicant has a current grant that will expire during the second round of study section review, the board suggestion results in an extension of the preexisting grant at its current funding level until the second review cycle is complete. The second benefit to the applicant is that rereview of an existing application means that it is unnecessary to prepare a new application.

Some generalizations can, of course, be made. Scientists who have been successful in the current review system view it more favorably that those who have not. There are opportunities within the system for reviewers to play favorites or to discharge ani-

mosities, but none of the experts that OTA talked with offered specific examples. The NIH system works well (27) in keeping applicants informed of what is happening to their proposals and of reasons for the decisions that are made.

Typically, criticisms of the peer review system are countered by arguments similar to those used to counter criticisms of democracy: Yes, there are problems, and, indeed, the system may be as bad as can be imagined, but it's better than anything else. OTA's conversations with experts generated four pointed criticisms of the NIH peer review system.

1. The research proposals that project 2, 3, or more years into the future are not worth the paper they are written on.
2. Narrowly focused, "can't miss" applications receive better scores than applications that are broader and, if successful, more important.
3. "Peers" on study sections are not scientifically equal to the applicants, and sitting on a study section allows second-rate scientists opportunities to steal ideas from applicants.
4. The NIH rules that a scientist can serve only one term on a study section is resulting in study section membership growing younger and younger. Younger scientists are not familiar with the difficulties and costs of running large-scale laboratories.

Directed at points 1 and 2 were comments that good investigators plan carefully, obtain results, and follow up leads. Narrow, carefully focused proposals are most accurate in predicting results. By analogy, it may also be that the authors of such applications are least-well prepared to generate or recognize unpredicted leads and follow them down unexpected courses. Of course, a breakthrough finding might occur in either broadly or narrowly focused research, but rapid exploitation is thought to be more likely in the former case.

Suggestions were made that NIH (and NSF) consider attaching greater weight to records of past accomplishments and less to projected research projects. Both the study of NSF peer review (15) and the GAO study of both NSF and NIH peer review (27) drew attention to the relatively small weight given to past performance. The NSF study, as has been mentioned, regarded that finding as "unexpected."

Published papers, which experts in the field, such as study section members, will have read anyway, provide a measure of scientists' accomplishments. Reliance on past performance, as judged from the scientific literature, should reduce the workload on reviewers, and at the same time, permit ranking of the applications. A grant supports a scientist's research efforts; how the scientist has done in the past is a guide to future production.

An immediate problem with "review" concentrating on past performance is how to judge the just-beginning investigator. Some experts expressed the opinion that "new" investigators are now treated differently from "established" ones. Study sections may be willing to take more of a chance on the new investigators. NIH estimates that one out of four scientists who are awarded an NIH research grant receives one and only one grant. This 25 percent includes both one-time grantees who do not submit another application ("dropouts") and individuals who resubmit and do not achieve a fundable priority score.

Opinions were expressed to the OTA staff that reviewers tend to judge more harshly applications that involve risk in the sense that an experiment may fail to produce the result that is predicted. Discussions about this point emphasized that poorly prepared or poorly thought through applications were not to be favored. "Fishing expedition" applications, which describe experiments to be done with little description of expected results and scanty information about the interpretation that will be placed on results were not held in high regard. On the other hand, concern was expressed that applications that posit a number of possible outcomes, even those prepared by well-regarded scientists, may not be given high grades in comparison to near repeats of already completed studies in which results can be predicted with greater certainty. The past production of good results and proper interpretation of those results, in the eyes of some, are a better guide to the future than proposed research.

Experts who discussed peer review with OTA staff pointed out that greater reliance on past performance would reduce concern about the third point mentioned above. Applications that describe the future in general terms would be a less rewarding source of intellectual plunder.

Finally, greater reliance on past performance would provide more time for research on the part of applicants and reviewers. The application could be shorter and require less preparation. The reviewer would have less to read.

Comments Made to OTA About Various Grant Mechanisms

The research project grant in support of an individual researcher's activities is the backbone of NIH research activities and is seen as the essential element in research support. In addition, some experts con-

tacted by OTA expressed great favor for program project grants. The arguments made for such support was that it concentrated the talents and experiences of several individuals on a single project. The common goal is seen as producing a research whole greater than its parts. Review of program projects includes a site visit by a study section members and NCI staff, and that activity was seen as making for better reviews.

The responses concerning center grants varied. Several experts think that center grant applications are so large and complex as to be almost impossible to review. There was also concern that poorer quality research and researchers might shelter inside center grant support. On the other hand, centers—because of their size and complexity—allow some research projects that cannot be supported by other mechanisms.

One respondent suggested that center grants might be made to exceptional scientist-administrators in much the same way as the Max Planck Institutes in Germany are funded. The center director would be responsible for hiring staff, reviewing and approving research efforts, and the productivity of the center. At the end of the grant support period, the center's performance would be judged by its publications and reputation. Such an approach would eliminate the cumbersome and, some suggest, ineffective review of center grant applications. It would also represent a giving-up of authority by NCI.

Conclusions.—The peer review and extramural research system, being fundamental to the success of NIH, have been studied, examined, and discussed. The result of almost all of the investigations has been confirmation that the system works. There have been no suggested alternatives. A contrast to that generally favorable conclusion is the finding about the lack of the draw in the review process.

Appendix C

NHLBI Clinical Trials

Introduction

The National Heart, Lung, and Blood Institute (NHLBI) has an extensive program of clinical trials dealing with critical issues in the prevention and treatment of heart, lung, and blood diseases. These contract programs now comprise about 9 percent of the NHLBI's extramural budget.

The investment in major clinical trials has grown since the early part of this decade to nearly $42 million for fiscal year 1981 (table C-1).

NHLBI's complement of clinical trials represents a balance among several factors. First, the trial must be in NHLBI's purview; that is, the design and management of the clinical trial must require NHLBI's research expertise. Some validation studies may be aimed at questions that are related solely to health services delivery, and consequently such experiments would not fall within NHLBI's purview, although the Institute would very likely be involved in an advisory capacity.

Second, the clinical trial must satisfy several requirements related to such factors as the scientific basis for the trial's underlying hypothesis and the potential impact of that trial. Through NHLBI's experience with clinical trials, these factors have been incorporated into a clinical trial decision process that divides the trial into four distinct phases—initiation, planning, recruitment and intervention, and analysis and dissemination of the trial results. Separating each phase is a crucial decision point at which NHLBI determines either to commit funds to the next stage of the clinical trial (the first two decision points) or to conclude the Intervention portion of the trial (the last decision point).

Tables C-2 and C-3 summarize data on the Institute's clinical trials. Table C-2 is a fiscal overview of the clinical trials, with the expected costs of the projects ranging from approximately $1 million to over $100 million. Table C-3 shows the broad characteristics of the clinical trials. The number of subjects ranges from very few—even as few as 100—up to almost 13,000 (for the Multiple Risk Factor Intervention Trial). The Institute's trials are currently in all phases of the clinical trial decision process; for example, the multicenter investigation of the limitation of infarct size (MILIS) is now in the recruitment and intervention phase, whereas the Hypertension Detection and Followup Program is in analysis and dissemination.

NHLBI's complement of clinical trials deals with both prevention of disease and treatment of disease. The primary prevention trials are testing interventions to prevent disease before biological onset; secondary prevention trials are testing intervention after the disease is detected but before it is symptomatic.

The following sections, taken from NHLBI's "Clinical Trials Briefing Document" (Jan. 27, 1982), summarize NHLBI's clinical trials program and are divided into: 1) recently completed trials; 2) recently initiated trials; and 3) trials in the planning stage.

Table C-1.

History of Major NHLBI Clinical Trials

(Dollars in Millions)

	FY 1972	FY 1973	FY 1974*	FY 1975	FY 1976†	FY 1977	FY 1978	FY 1979	FY 1980	FY 1981
Heart and Vascular Diseases										
HDFP	$ 3.97	$ 5.70	$11.05	$ 5.67	$12.65	$10.35	$ 7.85	$ 4.03	$ 3.43	$ 1.29
LRC	5.38	8.51	16.93	13.51	17.33	14.27	10.53	21.06	15.49	16.25
MRFIT	3.27	7.10	15.39	12.50	14.51	9.04	16.02	12.63	9.40	10.99
CASS	-	.10	.88	3.20	.87	2.85	4.59	1.78	4.44	2.40
ANIS	-	-	-	4.51	3.12	1.96	3.11	3.78	.37	-
BHAT	-	-	-	-	-	.54	3.72	5.99	3.85	3.80
MILIS	-	-	-	-	-	-	3.15	2.81	2.69	3.49
Subtotal, Heart and Vascular	12.62	21.41	44.24	39.40	48.48	39.01	48.97	52.08	39.67	38.31
Lung Diseases										
RDS Steroid Trials	-	-	-	-	.14	1.74	.32	1.49	.75	.45
Nocturnal Oxygen Therapy	-	-	-	-	.12	1.33	.91	1.24	.37	-
IPPB	-	-	-	-	-	.17	1.62	1.36	1.54	2.02
Subtotal, Lung	-	-	-	-	.26	3.24	2.86	4.09	2.66	2.47
Blood Diseases and Resources										
Factor VII	-	-	-	1.27	.04	.75	.69	.38	-	-
Granulocyte Studies	-	-	-	-	.30	.44	.36	.54	-	-
Subtotal, Blood	-	-	-	1.27	.35	1.19	1.05	.92	-	-
TOTAL NHLBI Major Clinical Trials	$12.62	$21.41	$44.24	$40.67	$49.09	$43.44	$52.88	$57.09	$42.33	$40.78

*Reflects release of fiscal year 1973 impounded funds.
†Includes Transition Quarter.
Note: Totals may not add due to rounding.

Source: National Heart, Lung, and Blood Institute

Table C-2.--Fiscal Overview of NHLBI Clinical Trials

CLINICAL TRIAL	COST TO DATE*	PROJECTED TOTAL COST
Division of Heart and Vascular Diseases		
Coronary Drug Project (CDP)	$ 41,760,030	$ 41,760,030
Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)	86,727,695	104,420,695
Multiple Risk Factor Intervention Trial (MRFIT)	110,833,165	115,769,176
Hypertension Detection and Follow-up Program (HDFP)	68,174,982	70,541,982
Unstable Angina Pectoris Trial	485,849	485,849
Coronary Artery Surgery Study (CASS)	21,115,393	25,147,393
Program on Surgical Control of Hyperlipidemias (POSCH)	20,591,097	28,750,516
Aspirin Myocardial Infarction Study (AMIS)	16,859,386	16,859,386
Beta-Blocker Heart Attack Trial (BHAT)	17,985,327	18,200,000
Multicenter Investigation of Limitation of Infarct Size (MILIS)	12,568,941	19,437,841
Treatment of Hypertension	3,126,004	3,126,004
Management of Patent Ductus in Premature Infants	4,120,095	4,120,095
Systolic Hypertension in the Elderly Program (SHEP)	2,036,251	3,550,000
Randomized Trial of Aspirin and Mortality in Physicians	506,002	2,372,155
Primary Prevention of Hypertension	1,121,387	10,933,250
Totals	$408,011,504	465,474,382

*As of September 30, 1981.

Table C-2 (continued)

CLINICAL TRIAL	COST TO DATE*	PROJECTED TOTAL COST
Division of Lung Diseases		
Neonatal Respiratory Distress Syndrome	$ 4,892,457	$ 5,567,457
Intermittent Positive Pressure Breathing (IPPB)	6,719,975	9,532,975
Nocturnal Oxygen Therapy	3,977,382	3,977,382
Extracorporeal Membrane Oxygenator Study (ECMO)	5,552,340	5,552,340
Totals	$ 21,141,154	$ 24,630,154
Division of Blood Diseases and Resources		
Granulocyte Transfusion Study	$ 1,635,142	$ 1,635,142
Interruption of Maternal to Infant Transmission of Hepatitis B by Means of Hepatitis B Immune Globulin	113,711	113,711
Cooperative Study of Factor VIII Inhibitors	782,350	782,350
Hepatitis B Vaccine Clinical Trial	200,000	200,000
Totals	$ 2,731,203	$ 2,731,203

*As of September 30, 1981

Table C-2 (continued)

CLINICAL TRIAL	COST TO DATE*	PROJECTED TOTAL COST
Division of Intramural Research		
NHLBI Type II Coronary Intervention Study	$ 444,378	$ 444,378
Diffuse Fibrotic Lung Disease	**	**
Evaluation of Subcutaneous Desferrioxamine as Treatment for Transfusional Hemochromatosis and a Controlled Trial on Ascorbic Acid	**	**
Totals	$ 444,378	$ 444,378
NHLBI Grand Totals	$432,328,239	$493,380,117

*As of September 30, 1981.

**The Division of Intramural Research is reported in man-years, not dollars. The NHLBI Type II Coronary Intervention Study is also supported by a contract.

Source: National Heart, Lung, and Blood Institute

Table C-3.--Ongoing and Recently Completed NHLBI Clinical Trials

CLINICAL TRIAL	SUBJECTS	STATUS	PROJECTED TOTAL COST
	Division of Heart and Vascular Diseases		
Coronary Drug Project (CDP): Secondary prevention of coronary heart disease with cholesterol-lowering drugs.	8,341 subjects followed for 5 to 8.5 years at 53 clinics.	Initiated in 1965. Recruitment and Intervention completed in 1975. Now in Analysis and Dissemination Phase.	$ 41,760,030
Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT): Primary prevention of coronary heart disease in hypercholesteremic patients with the cholesterol-lowering drug cholestyramine.	3,810 subjects followed for 7 years at 12 clinics.	Now in the Intervention phase, which is scheduled for completion in 1983.	104,420,695
Multiple Risk Factor Intervention Trial (MRFIT): Primary prevention of coronary heart disease by lowering serum cholesterol, reducing blood pressure, and reducing or eliminating cigarette smoking.	12,866 subjects followed for 6 years at 20 clinics.	Now in the Intervention phase, which is scheduled for completion February 28, 1982.	115,769,176
Hypertension Detection and Follow-up Program (HDFP): Evaluation of hypertension control to reduce total mortality	10,940 subjects followed for 9 years at 14 clinics.	Now in the Analysis and Dissemination Phase.	70,541,982

Table C-3 (continued)

CLINICAL TRIAL	SUBJECTS	STATUS	PROJECTED TOTAL COST
Division of Heart and Vascular Diseases (Continued)			
Unstable Angina Pectoris Trial: Secondary prevention of coronary heart disease by coronary artery bypass surgery or medical management in patients with unstable angina pectoris.	288 subjects followed for 9 years at 9 clinics.	Now in the Analysis and Dissemination Phase, which is scheduled for completion in 1982.	$ 485,849
Coronary Artery Surgery Study (CASS): Treatment of coronary heart disease by coronary artery bypass surgery or medical management in patients with stable angina.	780 subjects have been entered into this trial. Randomized patients to be followed for at least 4 years at 10 clinics. The study also includes a registry of 24,188 patients referred for coronary arteriography.	Recruitment ended in 1979. Follow-up is to extend for 5 years.	25,147,393
Program on Surgical Control of Hyperlipidemias (POSCH): Prevention of myocardial infarction and death in survivors of myocardial infarction by partial ileo bypass surgery.	Approximately 500 subjects have been recruited into this trial, which has a goal of 1,000 subjects. Patients are to be followed for 5 years at 4 clinics.	Now in the Recruitment and Intervention Phase.	28,750,516
Aspirin Myocardial Infarction Study (AMIS): Prevention of myocardial infarction and death in survivors of myocardial infarction with the drug aspirin.	4,524 subjects followed for 3 years at 30 clinics.	Now in the Analysis and Dissemination Phase.	16,859,386

Table C-3 (continued)

CLINICAL TRIAL	SUBJECTS	STATUS	PROJECTED TOTAL COST
Division of Heart and Vascular Diseases (Continued)			
Beta-Blocker Heart Attack Trial (BHAT): Prevention of myocardial infarction and death in survivors of myocardial infarction with the drug propranolol (a beta-blocker).	3,837 subjects followed for up to 3.5 years at 32 clinics.	Now in the Analysis and Dissemination Phase.	$ 18,200,000
Multicenter Investigation of Limitation of Infarct Size (MILIS): Treatment of myocardial infarction with the drugs propranonlol and/or hyaluronidase.	1,200 patients will be followed for 6 months in 5 clinics.	Now in the Recruitment and Intervention Phase, which is scheduled for completion in June, 1984.	19,437,841
Treatment of Hypertension: Primary prevention of cardiovascular morbidity and mortality by drug treatment of hypertension with chlorothiazide plus Rauwolfia serpentina.	389 subjects followed for up to 9 years at 6 clinics.	Initiated in 1966. Recruitment and intervention Phase completed in 1976. Now in the Analysis and Dissemination Phase.	3,126,004
Management of Patent Ductus in Premature Infants: Comparison of treatment of patent ductus arteriosus with the drug indomethacin or with surgery and conventional medical therapy.	400 subjects to be followed at 12 clinics for 1 year.	Now in the Intervention Phase, which is scheduled for completion in March, 1982.	4,120,095
Systolic Hypertension in the Elderly Program (SHEP): Prevention of stroke with standard antihypertensive agents	500 subjects to be followed at 5 clinics.	Now in the Recruitment and Intervention Phase. Recruitment will continue through June, 1982. All patients are to be followed through June, 1983.	3,550,000

Table C-3 (continued)

CLINICAL TRIAL	SUBJECTS	STATUS	PROJECTED TOTAL COST
	Division of Heart and Vascular Diseases (Continued)		
Randomized Trial of Aspirin and Mortality in Physicians. Primary prevention of cardiovascular disease by daily administration of aspirin.	21,900 subjects to be followed for 4.5 years.	Now in the Planning Phase.	$ 2,372,155
Primary Prevention of Hypertension. Primary prevention of hypertension with low sodium, high potassium diet or weight reduction.	900 subjects to be followed for 2 years at 4 clinics.	Now in the Planning Phase.	10,933,260
		Total DHVD	$465,474,392

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Table C-3 (continued)

CLINICAL TRIAL	SUBJECTS	STATUS	PROJECTED TOTAL COST
	Division of Lung Diseases		
Neonatal Respiratory Distress Syndrome: Primary prevention of neonatal respiratory distress syndrome by administering corticosteroids before birth.	696 subjects to be followed for 3 years in 5 clinics.	Now in the Follow-up Phase, which is scheduled for completion in March, 1983.	$ 5,567,457
Intermittent Positive Pressure Breathing (IPPB): Treatment of chronic obstructive pulmonary disease with intermittent positive pressure breathing compared with powered nebulizer.	985 subjects are to be followed for 3 years in 5 clinics.	Now in the the Interventions Phase, which is scheduled for completion in 1983.	9,532,975
Nocturnal Oxygen Therapy: Treatment of chronic hypoxic lung disease with 12-hour oxygen therapy compared with continuous low-flow oxygen therapy.	203 subjects followed for up to 30 months in 6 clinics.	Recruitment and Intervention completed in 1979. The trial has concluded.	3.977,382
Extracorporeal Support for Respiratory Insufficiency (ECMO): Treatment of acute respiratory failure with an extracorporeal membrane oxygenator.	90 subjects were followed for at least 5 days in 9 clinics.	Initiated in 1974. The Recruitment and Intervention Phase was completed in 1977. The trial has concluded.	5,552,340
		Total DLD	$ 24,630,154

Table C-3 (continued)

CLINICAL TRIAL	SUBJECTS	STATUS	PROJECTED TOTAL COST
Division of Blood Diseases and Resources			
Granulocyte Transfusion Study: Primary prevention and treatment of infection in patients undergoing chemotherapy for leukemia.	141 subjects followed for 3 years in 4 clinics.	Recruitment and Intervention ended in February 1980. Now in the Analysis and Dissemination Phase.	$ 1,635,142
Interruption of Maternal-to-Infant Transmission of Hepatitis B by Means of Hepatitis B Immune Globulin: Prevention of hepatitis B in infants.	205 subjects were followed for 3 years in 1 clinic.	Initiated in 1975. The Recruitment and Intervention Phase was completed in 1978. The trial is now complete.	113,711
Cooperative Study of Factor VIII Inhibitors: Factor IX treatment of persons with hemophilia A and inhibitors to Factor VIII.	51 subjects followed for varying lengths of time in 10 clinics.	The Intervention Phase was completed in late 1979. The trial has concluded.	782,350
Hepatitis B Vaccine Clinical Trial Vaccination of susceptible subjects with a vaccine which prevented hepatitis B1	1083 subjects followed for 2 years.	Initiated in 1978. Recruitment completed in October 1979. The trial has concluded.	200,000
		Total DBDR	$ 2,731,203

Table C-3 (continued)

CLINICAL TRIAL	SUBJECTS	STATUS	PROJECTED TOTAL COST
	Division of Intramural Research		
NHLBI Type II Coronary Intervention Study: Evaluation of lowering cholesterol with the drug cholestyramine in Type II hyperlipidemics in coronary artery disease regression.	143 subjects followed for 5 years at 1 clinic.	Now in the Analysis and Dissemination Phase which is scheduled for completion in 1982.	$ 443,378*
Diffuse Fibrotic Lung Disease: Treatment of idiopathic pulmonary fibrosis with cyclophosphamide compared with prednisone, or with dapsone or methylprednisolone. Treatment of sarcoidosis with short-term, high dose intravenous corticosteroids.	Approximately 150 subjects follwed for up to 1 year at 1 clinic.	Now in the Intervention Phase.	**
Evaluation of Subcutaneous Desferrioxamine as Treatment for Transfusional Hemochromatosis: Treatment of iron-overload with the agent desferrioxamine and ascorbic acid.	65 eligible subjects followed for up to 5 years at 2 clinics.	Now in the Recruitment and Intervention Phase.	**
		Total DIR	$ 444,378
		Total NHLBI	$493,280,117

*Contract costs only. Does not include Division of Intramural Research cost.

**The Division of Intramural Research is reported in man-years, not dollars.

Source: National Heart, Lung, and Blood Institute

II. Recently Completed Trials

HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM (HDFP)

Objective

To determine the effectiveness of systematic, sustained, antihypertensive therapy in reducing morbidity and mortality from hypertension in a wide spectrum of persons with elevated blood pressure in 14 communities. During its course, the trial also obtained a direct measure of prevalence, severity, and current treatment status of representative white and black populations with high blood pressure in these 14 communities, and obtained an estimate of the extent of attainable reduction of complications of high blood pressure by an organized screening and blood pressure management program.

Summary Data

Mechanism: Contract (Institute Initiated Clinical Trial)
Initiation: May 1971
Total Duration: 11 years (Intervention and Follow-up: 9 years)
Funding:

Total Support Prior to FY 1981	$66,890,877
FY 1981 Support	1,284,105
Support Projected Beyond FY 1981	2,367,000
Total Support	70,541,982

Subjects

Males and females, ages 30-69, representing 14 communities across the United States and the following ethnic groups: primarily white and blacks, some Latin Americans, and fewer than 1 percent Asian and American Indians. The total sample size is 10,940 persons. Individuals were randomized into the trial if average home readings and clinic readings of their diastolic pressure were equal to or above 95mm Hg and 90 mm Hg, respectively.

Experimental Design

The trial was a randomized, non-blind, fixed sample trial with single intervention and control groups. The intervention group received stepped care from the clinical trial clinics (see Background, below), while those in the control group were referred to their own physicians. Each community contributed both stepped care and referred care participants, but for analysis purposes, the groups were pooled into two groups. The primary endpoint was mortality. The effects of stepped vs. referred care were also assessed on intermediate and secondary factors, including specific causes of mortality, nonfatal myocardial infarction, stroke, hypertensive heart disease, congestive heart failure, and EKG abnormalities.

Current Phase (As of October 1981) Analysis and Dissemination

Hypertension Detection and Follow-up Program (HDFP)

Background

Published data from the Veterans Administration Cooperative Study of Hypertension demonstrated that reduction in morbidity and mortality could be attained by treating men with fixed diastolic blood pressure over 105 mm Hg. Similar trends occurred for those with fixed diastolic blood pressure between 90 and 104 mm Hg. Results and current trends from other studies supported these findings. However, prior to inception of the Hypertension Detection and Follow-up Program (HDFP), it was not known whether benefits from antihypertensive therapy applied to all hypertensives in the general population and whether making use of existing medical knowledge could significantly reduce morbidity and mortality from hypertension in communities.

Recognizing this need, NHLBI initiated the pilot activities of the HDFP to characterize significant operational, socioeconomic, and motivational or behavioral factors that would influence the acceptance of antihypertensive therapy in the defined populations within which the controlled clinical trial would take place and to obtain baseline information necessary to the undertaking of the clinical trial.

The planning of the trial, including the development of a protocol and manual of operations, began in 1971. Between February 1973 and May 1974, 158,906 persons were screened for high blood pressure in 14 communities. A total of 10,940 hypertensive participants were randomized.

The primary hypothesis tested by this clinical trial was that intensive blood pressure control under stepped care for 5 years can significantly reduce mortality compared with that under referred care. Stepped care is the method of treatment in HDFP clinics in which a diuretic is given initially and additional antihypertensive agents are added in a time-structured, stepwise fashion until goal blood pressure is achieved. Referred care represents referral to private physicians and other community sources of care. Participating in this study were 14 clinical centers, a coordinating center, EKG center, central laboratory, and monitoring laboratory.

The intervention portion of the trial has been completed. The study is being extended through May 1982 in order to continue the surveillance of mortality and blood pressure control.

Trial Results

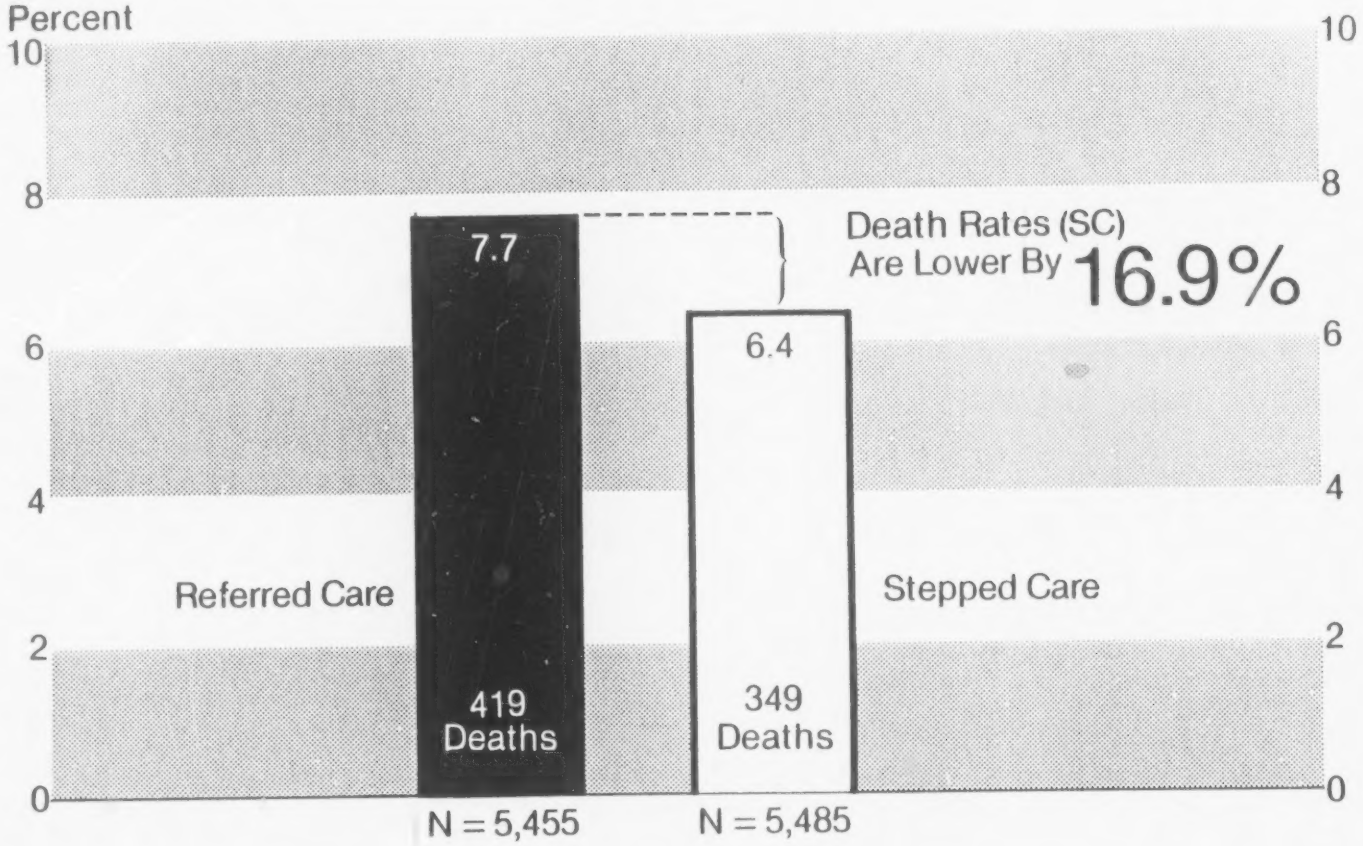
The following statements have been abstracted from papers appearing in the Journal of the American Medical Association.*

- Five-year mortality from all causes was 17 percent lower for the stepped-care group compared with the referred-care group (see Figure 3) and 20 percent lower for the stepped-care participants with "mild" hypertension (diastolic blood pressure 90-104 mm Hg) compared with the corresponding referred-care subgroup.

Figure C-1.--

Mortality - All Causes

5-Year Mortality Rates (%) From All Causes for
Stepped Care (SC) and Referred Care (RC) Participants



Hypertension Detection and
Follow-up Program (HDFP)

- Preliminary data on cause-specific mortality indicate that the number of deaths from cerebrovascular disease was smaller by almost 45 percent for the stepped-care group. There were 26 percent fewer deaths from acute myocardial infarction in the stepped-care group. Death rates from other ischemic heart disease were similar in both groups. Nine deaths in the stepped-care group were certified to hypertension compared with 14 in the referred-care group. For all cardiovascular causes, there were 19 percent fewer deaths for the stepped-care group than for the referred-care group.

- For white men, black men, and black women and for age subgroups 50 to 59 and 60 to 69, 5-year all-cause death rates were substantially lower--by 15 percent to 28 percent--for the stepped-care subgroups compared with the referred-care subgroups.

- Blood pressure control was consistently better for the stepped-care group than for the referred-care group. After 5 years, 64.9 percent of the stepped-care participants had reached goal diastolic blood pressure versus 43.6 percent of the referred-care participants. Goal diastolic blood pressure was defined as 90 mm Hg for those entering with DBP equal to or greater than 100 or receiving antihypertensive therapy, and a 10 mm Hg decrease for those entering with DBP 90-99. After 5 years, 63.8 percent of those stepped-care participants in stratum I (DBP 90-104) achieved goal diastolic blood pressure versus 43.0 percent of those in referred-care. Also, after 5 years, 69.6 percent of stepped-care participants in stratum II (DBP 105-114) achieved goal diastolic blood pressure versus 48.3 percent of those in referred-care and 63.6 percent of stepped-care participants in stratum III (DBP 115 or higher) achieved goal diastolic blood pressure versus 39.1 percent of referred-care participants.

- Systematic, effective management of hypertension has great potential for reducing mortality for the large numbers of people with hypertension in the population, including those with "mild" hypertension.

*Hypertension Detection and Follow-up Program Cooperative Group: Five-year Findings of the Hypertension Detection and Follow-up Program: I. Reduction in Mortality of Persons with High Blood Pressure, Including Mild Hypertension. JAMA 242:2562-2571, 1979.

Hypertension Detection and Follow-up Program Cooperative Group: Five-Year Findings of the Hypertension Detection and Follow-up Program: II. Mortality by Race-Sex and Age. JAMA 242:2572-2577, 1979.

ASPIRIN-MYOCARDIAL INFARCTION STUDY (AMIS)

Objective

To determine whether the daily administration of 1 gm of aspirin to individuals with a documented myocardial infarction will result in a significant reduction in mortality over a 3-year period.

Summary Data

Mechanism: Contract (Institute Initiated Clinical Trial)
Initiation: October 1974
Total Duration: 6 years (Intervention: minimum 3 years)
Funding:

Total Support Prior to FY 1981	$16,859,386
FY 1981 Support	0
Support Projected Beyond FY 1981	0
Total Support	$16,859,386

Subjects

Males and females, ages 30-69, not stratified as to ethnic group, with a documented myocardial infarction.

Experimental Design

Randomized, double-blind, fixed sample. Eligible patients were assigned to a treatment group receiving 1 gm of aspirin daily (the equivalent of three standard aspirin tablets) or to a control group receiving a placebo.

Current Phase (As of October 1981): Analysis and Dissemination

Background

It has been postulated that thrombosis plays a major role in the late stages of coronary artery occlusion. Platelet aggregation is a large component in the formation of arterial thrombi. Theoretically, an agent which prevents the aggregation of platelets would be of value in people with coronary artery disease. Aspirin, in small doses, inhibits platelet aggregation for prolonged periods of time, and therefore might be expected to prevent or retard the occlusion of coronary arteries. This would be reflected in a decrease in the incidence of myocardial infarction and a decrease in mortality due to coronary artery disease.

Several studies had given preliminary evidence that regular administration of aspirin may be of benefit to patients with known the Coronary Drug Project, ran a pilot trial of aspirin and placebo in men with previous myocardial infarctions. Preliminary results from this trial demonstrated its feasibility and led NHLBI to sponsor a more definitive controlled study of the benefit of aspirin in the secondary prevention of coronary heart disease.

Aspirin-Myocardial Infarction Study (AMIS)

An Institute Planning Committee developed a protocol, manual of operations, and data collection forms. Recruitment of patients began in June 1975, with the first patient randomized on July 2, 1975. Patients who were randomized had been seen at the AMIS Clinical Center for two initial visits and one baseline visit and were free of any reasons for exclusion, such as the current use of anticoagulants and a history of adverse reactions to aspirin. Patients took acetaminophen at times when they would normally take aspirin.

Follow-up was for a minimum of 3 years, with each patient seen at 4-month intervals and monitored for side effects and various nonfatal events, including cardiovascular problems. The primary endpoint was mortality. Annually, a detailed history was obtained and a complete physical examination performed. The study involved 30 clinical centers, a coordinating center, and a central laboratory.

The study completed patient recruitment in the scheduled 1-year period. A total of 4,524 post-MI patients were enrolled by the 30 clinical centers. Three-year minimum patient follow-up ended in June 1979.

Trial Results

- Total mortality during the entire follow-up period was 10.8 percent in the aspirin group and 9.7 percent in the placebo group.
- Three-year mortality was 9.6 percent in the aspirin group and 8.8 percent in the placebo group.
- The rate of definite nonfatal MI was 8.1 percent in the placebo group and 6.3 percent in the aspirin group.
- Coronary incidence (coronary heart disease mortality or definite nonfatal MI) was 14.1 percent in the aspirin group and 14.8 percent in the placebo group.
- Symptoms of peptic ulcer, gastritis, or erosion of gastric mucosa occurred in 23.7 percent of the aspirin group and 14.9 percent of the placebo group.
- Based on AMIS results, aspirin is not recommended for routine use in patients who have survived a myocardial infarction.

BETA-BLOCKER HEART ATTACK TRIAL (BHAT)

Objective

To determine whether the regular administration of the beta-blocker drug propranolol to people who have had at least one documented myocardial infarction will result in a significant reduction of mortality from all causes over the follow-up period. A total of 3,837 eligible volunteer patients were recruited to participate in a double-blind clinical trial within 5 to 21 days after the onset of the acute event. One-half of the patients were randomly assigned to a beta-blocking drug (propranolol) and one-half to a placebo. The trial also evaluated the effect of propranolol on incidences of coronary heart disease mortality, sudden cardiac death, and nonfatal myocardial infarction plus coronary heart disease mortality in persons with documented previous myocardial infarction.

Summary Data

Mechanism: Contract (Institute Initiated Clinical Trial)
Initiation: September 1977
Total duration: 7 years (Intervention: 1-3.5 years)
Funding:

Total Support Prior to FY 1981	$14,098,633
FY 1981 Support	3,886,694
Support Projected Beyond FY 1981	214,673
Total Support	18,200,000

Subjects

Males and females, ages 30-69, who have had at least one myocardial infarction. Subjects were not stratified as to ethnic group and were drawn from various locations in the United States. Total sample size equaled 3,837. Individuals were randomized to treatment and control groups.

Experimental Design

A randomized, double-blind design with single experimental and control groups. Patients were recruited while in the hospital for an acute myocardial infarction and enrolled in the study before discharge. Eligible patients fulfilled the study definition of an acute myocardial infarction. The diagnosis was based either on electrocardiographic records showing evolving QRS segment changes or on ST segment and T wave changes together with enzyme changes and appropriate clinical history. One-half of the patients were placed on therapy using a beta-blocking drug (propranolol). The other half received a placebo. Intervention duration was 1-3.5 years.

Current Phase (As of October 1981): Analysis and Dissemination

Beta Blocker Heart Attack Trial (BHAT)

Background

Coronary heart disease and its complications account for over 600,000 deaths in the U.S. each year. Survivors of a documented myocardial infarction are recognized as having a high risk of dying relative to the general population. Serious arrhythmias, occurring with or without evidence of new infarction, are a common cause of death in this population. Theoretically, an agent which (1) can block the sympathetic nervous activity thought to be involved in precipitating sudden death and (2) has non-neurogenic antiarrhythmic properties would be of value to people with coronary heart disease. Propranolol, like other beta-blocking agents, has these as well as other properties and therefore might be expected to prevent or retard complications of coronary heart disease such as serious arrhythmias. This would be reflected in a decrease in mortality due to coronary heart disease.

A workshop on chronic antiarrhythmic therapy held in 1976 reviewed contemporary experimental data and clinical practice and recommended that a clinical trial be undertaken to clearly show the effects of beta-blocking drugs on mortality. Subsequently, such a trial was approved by the Clinical Applications and Prevention Advisory Committee, by the Cardiology Advisory Committee, and by the National Heart, Lung, and Blood Advisory Council.

The study protocol was reviewed in February 1978 and recommended for approval by the policy-data monitoring board and ad hoc members. The protocol was approved by the Director of NHLBI in March 1978. Recruitment started on June 19, 1978 and ended in October 1980. A total of 3,837 patients were randomized. Participating in the trial were 32 clinical centers, an EKG center, a central laboratory, a coordinating center, a 1-hour ambulatory EKG center, a 24-hour ambulatory EKG center, and and EKG tape quality control center.

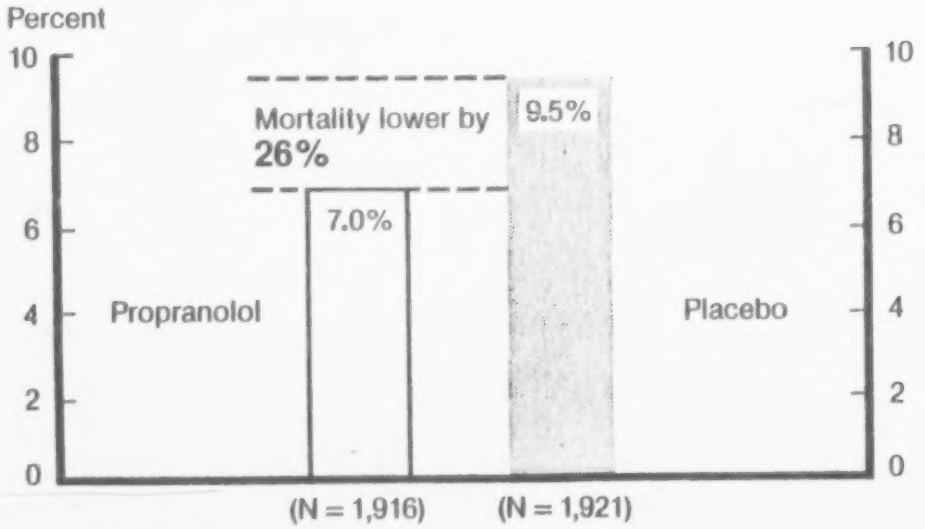
Trial Results

On the recommendation of the Policy and Data Monitoring Board, intervention was ended in October 1981 instead of in June 1982. Mortality was 9.5% in the placebo group and 7.0% in the propranolol group, a reduction of 26% (see Figure 4). Preliminary results of the trial indicate that the beneficial efforts of propranolol occur primarily in the first year after a myocardial infarction.

Figure 4

Beta-Blocker Heart Attack Trial

TOTAL MORTALITY
(Average 24-Month Follow-up)



PREVENTION OF NEONATAL RESPIRATORY DISTRESS SYNDROME WITH ANTENATAL STEROID ADMINISTRATION

Objective

To determine the effect of corticosteroids, administered 24 to 48 hours before parturition, on the incidence of neonatal respiratory distress syndrome (RDS) and to determine whether the therapy has any adverse short- or long-term (up to 36 months) effects on the infant. Secondarily, to determine whether the therapy has any adverse short-term effects on the mother and to determine whether morbidity rates for neonatal respiratory distress syndrome as well as total and cause-specific infant mortality rates differ between mothers who received antenatal steroids and those who received conventional medical care.

Summary Data

Mechanism: Contract (Institute Initiated Clinical Trial)
Initiation: June 1976
Total Duration: 6 years (Intervention: 48 hours; Follow-up: 36 months)

Funding:

Total Support Prior to FY 1981	$4,438,366
FY 1981 Support	454,091
Support Projected Beyond FY 1981	675,000
Total Support	$5,567,457

Subjects

Male and female fetuses and infants; pregnant women with anticipated premature delivery and gestational age between 26 and 37 weeks.

Experimental Design

Randomized, double-blind, fixed sample. Six hundred and ninety-six patients were randomized to four doses of dexamethasone every 12 hours or to placebo. Endpoints were the incidence of respiratory distress syndrome and abnormality of motor-neuro-intellectual development.

Current Phase (As of October 1981) Intervention (Follow-up)

Background

Neonatal respiratory distress syndrome is one of the leading causes of disability and death in the newborn. In the United States, approximately 10 percent of all infants are premature, and each year about 50,000 cases of neonatal respiratory distress syndrom occur. Hospital costs at the onset of the trial averaged $5,000 per patient, with an average stay of 23 days.

Prevention of Neonatal Respiratory Distress Syndrome with Antenatal Steroid Administration

Extensive studies in animal models on respiratory distress syndrome have demonstrated that antenatal administration of synthetic (dexamethasone) and natural (cortisol) corticosteroids accelerates lung maturation and significantly diminishes the occurrence of RDS. Only one large, controlled, double-blind clinical trial on antenatal corticosteroid therapy has been published to date, although this therapy is beginning to be widely used in the United States. In that trial, which was conducted in New Zealand, it was reported that there is a lower-than expected incidence of neonatal RDS when betamethasone is given to mothers for at least 24 hours after the onset of premature labor and not later than the 32nd week of gestation. No follow-up data, however, have been published. Although a variety of conditions in newborn infants have been treated with steroids over the past 20 years without adverse effects, investigations have been needed on the short-term effects of corticosteroids administered antenatally on neonate and mother and on the long-term effects on the infants.

The Planning Phase of this trial was completed in March 1977, with formulation of a common protocol and manual of operations. Patient screening and enrollment began in May 1977 and ended on March 1, 1980. Follow-up will continue for 36 months after the entrance of the last patient. At the present time, there are five clinical centers and a coordinating center in the trial.

Preliminary Trial Results

Fetal and neonatal death rates were not significantly altered by treatment. Fetal death rate was 1.6% in the treatment group and 2.2% in the placebo group. Neonatal death rate before 40 weeks of age was 9.3% in the treatment group and 8.8% in the placebo group. The overall incidence of RDS was different between control subjects (18.0%) and treated mothers (12.6%). This effect was mainly due to the pronounced beneficial effect of treatment on singleton female infants. No treatment effect was observed in male infants. Non-Caucasians were improved, whereas Caucasians showed little benefit.

CORONARY DRUG PROJECT

Objective

To determine whether the regular administration of lipid modifying drugs (clofibrate, nicotinic acid, estrogen, dextrothyroxine) to men with a documented myocardial infarction would result in significant reduction in total mortality over a 5-year period. Secondarily, to determine whether the degree to which these drugs change serum lipids is correlated with any effect on mortality and morbidity rates; to gain further information on the long-term prognosis of myocardial infarction (by studying the control group as intensively as the treatment group); to acquire further experience and knowledge concerning the techniques and methodology of long-term clinical trials; to determine, in a substudy, the effectiveness of aspirin, a platelet inhibitor, in reducing recurrences of myocardial infarction.

Summary Data

Mechanism: Grant (Investigator Initiated Clinical Trial)
Initiation: April 1965
Total Duration: 16 years (Intervention: 5-8.5 years*)
Funding:

Total Support Prior to FY 1981	$41,590,050
FY 1981 Support	169,980
Support Projected Beyond FY 1981	0
Total Support	$41,760,030

Subjects

Males, ages 30-64, not stratified as to ethnic group, who were 3 months beyond their most recent myocardial infarction.

Experimental Design

Randomized, double-blind, fixed sample. A total of 8,341 patients were randomly assigned to six treatment groups consisting of 2.5 mg/day of conjugated estrogens, 5.0 mg/day of conjugated estrogens, 1.8 gm/day of clofibrate, 6.0 mg/day of dextrothyroxine sodium, 3.0 gm/day of niacin, or 3.8 gm/day of lactose placebo.

Current Phase (As of October 1981): Nearly concluded, small Analysis and Dissemination effort underway.

Background

Correlation of high levels of serum cholesterol with an increased incidence and prevalence of coronary heart disease (CHD) was demonstrated--prior to the inception of the Coronary Drug Project--repeatedly in prospective and cross-sectional epidemiological surveys (e.g., the Tecumseh Study, the Framingham Heart Disease Study). These findings led to the question of

*Applies to clofibrate and niacin therapy. Estrogen and dextrothyroxine treatments were discountinued early.

whether long-term lowering of serum lipids in individuals both with and without CHD would have a beneficial effect on morbidity and mortality. The Coronary Drug Project was designed to answer the question of secondary prevention. In 1961, Dr. Robert Wilkins (Boston University School of Medicine) chaired an ad hoc committee which determined the desirability and feasibility of the conduct of this study. Following National Heart Advisory Council (NHAC) support, a study Policy Board, Steering Committee, and Coordinating Center were established and a detailed protocol was written. In 1964, NHAC approved the project and the NHI recommendation for implementation; the study was begun in 1965. Supported by the grant mechanism, the trial involved 53 participating clinics, a coordinating center, central laboratory, ECG center, drug procurement and distribution center, and NHI medical liaison office, and a policy board, steering committee, and 12 other committees (e.g., a data and safety monitoring committee).

The first patient was randomly allocated to treatment in March 1966 and the last in October 1969. Each patient reported to the clinic every 4 months for a follow-up visit.

Trial Results

Three drug regimens were discontinued before the scheduled completion of the project. The 5.0 mg/day estrogen regimen was discontinued in 1970 because of the number of nonfatal cardiovascular events when compared with placebo and lack of evidence of efficacy with respect to the primary endpoint of total mortality. Dextrothyroxine sodium was discontinued in 1971 because of excess mortality in the treatment group as compared with the placebo group. The third regimen 2.5 mg/day of estrogen, was discontinued in 1973.

Findings in the nicotinic acid and clofibrate treated groups were that

- both drugs produced modest reduction in serum cholesterol concentrations,
- neither significantly decreased mortality compared with that of patients receiving placebo, and
- both drugs were associated with unpleasant and hazardous side effects* which affected both the cardiovascular and digestive systems.

These negative findings refer only to secondary prevention--to patients who have had one or more previous heart attacks--and do not indicate whether either clofibrate or nicotinic acid is useful for individuals who have not had a heart attack (i.e., for primary prevention).

*Clofibrate was associated with a high degree of cardiovascular morbidity. Nicotinic acid decreased angina and new heart attacks, but was associated with frequent side effects.

The study was extremely worthwhile in several respects:

- The trial established the hazardous side effects of the lipid-lowering drugs under test. Had the trial not been performed, these side effects might still be attributed to the natural course of the disease rather than to the drugs.
- The information obtained on the natural history of myocardial disease is extremely valuable and useful.

The trial also serves as the foundation for the primary prevention trials now underway.

The vital status as of March 1, 1980 of all participants alive at the end of the Coronary Drug Project is currently being examined. The objective is to confirm or refute reports of continued adverse effects on mortality of clofibrate years after cessation of use of the drug. This mortality surveillance will be conducted from June 1981 - June 1982 by the Coordinating Center.

UNSTABLE ANGINA PECTORIS TRIAL

Objective

To compare the efficacy of medical or surgical (coronary artery bypass graft) therapy with regard to survival and quality of life in patients with unstable angina and requisite coronary anatomy as defined by angiography.

Summary Data

Mechanism: Contract and Grant (Institute Initiated Clinical Trial)
Initiation: January 1972
Total Duration: 10 years (Intervention: 2 years)
Funding:

Total Support Prior to FY 1981	$485,849
FY 1981 Support	0
Support Projected Beyond FY 1981	0
Total Support	$485,849

Subjects

Males and females, ages 21 to 65, from selected sites across the United States. All subjects had class III or IV angina pectoris in which pain occurred at rest or with minimal exercise.

Experimental Design

Randomized, non-blind, sequential design with a control group and an experimental group. The patients in the experimental group were treated with coronary bypass surgery. Patients in the control group received intensive medical management. Endpoints were mortality and morbidity measures, such as incidence of myocardial infarction and persistence of angina.

Current Phase (As of October 1981): Analysis and Dissemination

Background

Angina pectoris is a symptomatic condition of attacks of chest pain, often debilitating. It is caused by a decreased supply of blood to the heart, such as that which might occur in coronary artery disease. The usual treatment of angina pectoris is designed to relieve the symptoms. It includes avoidance of activities that produce the discomfort and the use of nitroglycerin and beta-blocking drugs. Soon after the introduction of coronary bypass surgery, many doctors enthusiastically adopted this approach in treating patients with unstable angina.

In 1972, emphasizing that there was no definitive evidence showing the superiority of intensive medical management or coronary bypass surgery in determining mortality and morbidity in patients hospitalized with unstable angina, some of the participating groups in the NHLBI Myocardial Infarction Research Units developed a cooperative clinical trial to compare these medical and surgical approaches to therapy.

Unstable Angina Pectoris Trial

From 1972 through 1976, 288 patients were entered into this randomized clinical trial. One hundred forty-seven patients received intensive pharmacological medical therapy, and 141 comparable patients underwent coronary artery bypass surgery. Careful follow-up studies were performed on patients in both groups, in-hospital and during the post-hospital phase. These studies included, apart from routine physical examinations, resting electrocardiograms, chest x-ray films, and grade exercise tolerance tests at six months and twelve months.
Unstable Angina Pectoris Trial

Trial Results

During the study period, the hospital mortality rate was 5 percent in the surgical group and 3 percent in the medical group (difference not significant).* The rate of in-hospital myocardial infarction was 17 and 8 percent in the respective groups ($P<0.05$). In the last 4 years of the study (1973 to 1976), the hospital mortality rate decreased to 3 percent in the surgical group and to 2 percent in the medical group (difference not significant). During the last 3 years of the study (1974 to 1976), the rate of in-hospital myocardial infarction was 13 percent in the surgical group and 10 percent in the medical group (difference not significant). There were no differences in the subsets of patients with one-, two-, or three-vessel disease.

In the first year after hospital discharge, class III or IV angina (New York Heart Association criteria) was more common in medically than in surgically treated patients with one-vessel disease (22 percent versus 3 percent, $P<0.05$), two-vessel disease (40 percent versus 13 percent, $P<0.01$), and three-vessel disease (40 percent versus 15 percent, $P<.01$). During an average follow-up period of 30 months, 36 percent of the medically treated patients later underwent surgery to relieve unacceptable angina. Late mortality was comparable in the two groups, but the large number of medically treated patients who later underwent surgery prevents definitive conclusions about the relative effect of medical and surgical therapy on long-term mortality. However, the patients who responded to medical therapy did not have a higher rate than surgical patients.

The results indicate that patients wth unstable angina pectoris can be managed acutely with intensive medical therapy, including the administration of propranolol and long-acting nitrates in phamacologic doses, with adequate control of pain in most patients and no increase in early mortality or myocardial infarction rates. Later, elective surgery can be performed with a low risk and good clinical results if the patient's angina fails to respond to intensive medical therapy.

*Unstable Angina Pectoris Study Group: Unstable Angina Pectoris National Cooperative Study Group to Compare Medical and Surgical Therapy. II. In-Hospital Experience and Initial Follow-up Results in Patients with One-, Two-, and Three-Vessel Disease. Am. J. Cardiol. 42:839-848, 1978.

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NOCTURNAL OXYGEN THERAPY

Objective

To compare the efficacy of long-term use of nocturnal oxygen therapy (12 hours) with that of continuous, low-flow oxygen therapy (24 hours) in patients with chronic hypoxic lung disease.

Summary Data

Mechanism: Contract (Institute Initiated Clinical Trial)
Initiation: July 1976
Total Duration: 4 years
Funding:

Total Support Prior to FY 1981	$3,977,382
FY 1981 Support	0
Support Projected Beyond FY 1981	0
Total Support	$3,977,382

Subjects

Males and females, ages 35-70, not stratified as to ethnic group, who have severe chronic obstructive lung disease requiring supplemental oxygen therapy.

Experimental Design

Randomized, fixed sample. Two hundred and three patients were randomly assigned to at-home treatments of continuous oxygen therapy or nocturnal oxygen therapy. Endpoints related to quality of life, neuropsychological function, and respiratory function and capacity. Intervention lasted for 6 months to 3 years, with an average intervention of 19.3 months.

Current Phase (As of October 1981); Concluded

Background

Chronic obstructive pulmonary disease is a major health problem in the United States. In 1975, it was the sixth leading cause of death. The economic impact of the disease in 1972 amounted to $803 million in the direct costs of disability treatment, $3.05 billion in disability costs, and $645 million in lost earnings due to premature death.

Motivated in part by the significant toll of this disease, a conference on the Scientific Basis of Respiratory Therapy, co-sponsored by the American Thoracic Society and the Division of Lung Diseases, examined the current status of the use of oxygen therapy in chronic lung disease. The proceedings of the conference, published in the American Review of Respiratory Disease (Vol. 110, No. 6, December 1974), included a recommendation for clinical studies that would provide a critical assessment of the role of nocturnal oxygen therapy in the treatment of patients with chronic obstructive pulmonary disease. Low-flow oxygen, administered continuously, is known to benefit some patients with chronic hypoxic lung disease. However, low-flow oxygen administration for long

periods of time is cumbersome, confining, and expensive. If nocturnal oxygen administration could be unequivocally demonstrated to be efficacious, then the advantages of convenience and cost would have a favorable impact on treatment of patients, and a rationale could be developed for testing this therapy in a larger group of patients.

The Planning Phase of the trial was initiated in September 1976. Patient recruitment began in May 1977. The Recruitment Phase lasted 24 months. The 203 patients in the trial were assigned randomly to home treatments with nocturnal oxygen therapy or continuous low-flow oxygen therapy. The Recruitment and Intervention Phase has ended. The trial has now concluded.

Trial Results

Mortality in the nocturnal oxygen therapy group was nearly twice that in the continuous oxygen therapy group.* Sixty-four patients died, 41 in the nocturnal oxygen therapy group and 23 in the continuous oxygen therapy group. The 12-month mortality rate was 20.6 percent in the nocturnal oxygen therapy group and 11.9 percent in the continuous oxygen therapy group; 24-month mortality was 40.3 percent and 22.4 percent, respectively. Overall mortality was 31.5 percent for all patients.

The reason for the decreased mortality associated with continuous oxygen therapy is unclear. Only two of the numerous physiological and psychological variables showed a significant treatment-related change with time. Hematocrit value decreased in patients on continuous oxygen therapy, but not in those on nocturnal oxygen therapy. Although continuous oxygen therapy decreased hematocrit values and increased survival, there is no evidence that these results are related to one another. Pulmonary vascular resistance also showed a differential effect of treatment. However, the data suggest that although continuous oxygen therapy reduced both mortality and pulmonary vascular resistance, the two phenomena were not related.

*Nocturnal Oxygen Therapy Trial Group: Continuous or Nocturnal Oxygen Therapy in Hypoxemic Chronic Obstructive Lung Disease: A Clinical Trial. Ann. Intern. Med. 93:391-398, 1980.

EXTRACORPOREAL SUPPORT FOR RESPIRATORY INSUFFICIENCY (ECMO)

Objective

To evaluate indications for the use and efficacy of extracorporeal membrane oxygenators (ECMO's) for the support of patients with potentially reversible acute respiratory failure.

Summary Data

Mechanism: Contract (Institute Initiated Clinical Trial)
Initiation: June 1974
Total Duration: 3 years
Funding:

Total Support Prior to FY 1981	$5,552,340
FY 1981 Support	0
Support Projected Beyond FY 1981	0
Total Support	$5,552,340

Subjects

Males and females, ages 12 to 65, not stratified as to ethnic group, who had potentially reversible acute respiratory failure.

Experimental Design

Randomized, non-blind, fixed sample; 90 eligible patients were randomly assigned to a group receiving extracorporeal membrane oxygenation plus conventional therapy or to a group receiving conventional therapy.

Current Phase (As of October 1981): Concluded

Background

The report of the Task Force on Respiratory Diseases identified a clinical syndrome of acute respiratory insufficiency (ARI) and estimated that approximately 60,000 Americans die of ARI yearly. ARI was not precisely defined; indeed, the Task Force realized that pathologists do not recognize ARI. The Task Force pointed out that no diagnostic tests for early detection of ARI exist, that the incidence and prevalence of the disease are not known, and that existing therapy is supportive and nonspecific (diuretics, corticosteroids, etc.). The pathogenesis of the syndrome, the mechanism of interstitial edema, the defenses of the lung against agents causing ARI, and the ultrastructural pathology and natural history of the disease were virtually unknown. The Task Force indicated a need for Respiratory Care Centers with highly trained personnel that could reduce mortality from ARI.

This clinical trial grew out of the Task Force report. Nine participating centers defined ARI in clinical and physiological terms and agreed to a prospective randomized control study for 3 years to compare treatment of severe ARI by conventional means with treatment by extracorporeal membrane oxygenators.

Extracorporeal Support for Respiratory Insufficiency (ECMO)

Animal studies have shown that ECMO's can provide one to two weeks' support for the lungs without serious blood damage, in contrast to bubble oxygenators, which allow complete pulmonary bypass for approximately 6 hours, after which severe blood damage occurs at the direct blood-gas interface. If patients with hypoxia secondary to acute reversible lung injury can be supported with ECMO's until the lung lesion heals, improvement in survival rates and avoidance of the hazards of conventional therapy may result. The trial, now completed, was conducted at nine clinical centers in the United States.

Trial Results

Among the 90 patients in the randomized study, mortality for all groups was over 90 percent, and there were an equal number of survivors in the group receiving conventional therapy alone and in the group receiving extracorporeal membrane oxygenation plus conventional therapy. Morphological studies of biopsy and autopsy material from the study group support the view that, despite sophisticated technology, the progression of lung disease in patients with severe acute respiratory failure cannot be arrested by the use of ECMO.

GRANULOCYTE TRANFUSION STUDY

Objective

To evaluate granulocyte transfusion therapy with respect to its prophylactic and therapeutic effectiveness to prevent and aid recovery from infection. The study trials were conducted simultaneously.

Summary Data

Mechanism: Contract (Institute Initiated Clinical Trial)
Initiation: September 1976
Total Duration: 4 years
Funding:

Total Support Prior to FY 1981	$1,635,142
FY 1981 support	0
Support Projected Beyond FY 1981	0
Total Support	$1,635,142

Subjects

Prophylactic Trial: males and females, 12 years or older, who were in the first induction phase of chemotherapy for acute leukemia, who had severe neutropenia, and who did not have documented infection.

Therapeutic Trial: males and females, any age who were receiving chemotherapy for acute leukemia or who may have had aplastic anemia, who had severe neutropenia, and who had documented infection.

Experimental Design

Prophylactic Trial and Therapeutic Trial: randomized, non-blind, sequential. eligible patients were randomized to daily granulocyte transfusions or no granulocyte transfusions.

Current Phase (As of October 1981): Analysis and Dissemination

Background

Infection remains a major cause of death in patients receiving chemotherapy for malignant diseases. One approach to the problem of septicemia and high mortality in these patients is the therapeutic use of granulocyte tranfusions. Recent improvements in collection techniques, employing continuous flow centrifugation, now permit the collection of granulocytes from a single, normal donor in sufficient numbers to study their application in the treatment of infections in granulocytopenic patients. Recent studies have demonstrated the efficacy of granulocyte transfusions as an adjunct in the therapy of septicemia due to gram negative microorganisms associated with granulocytopenia.

The aims of the study were to determine (1) whether infections can be prevented in patients who receive granulocytes prophylactically and (2) whether recovery from infection is aided in patients who receive granulocytes therapeutically. Both trials utilized controls who received no granulocytes.

Granulocyte Transfusion Study

Four contracts were awarded in September 1976. The protocol designed to evaluate the efficacy of prophylactic granulocyte transfusions was completed at the close of 1977. The protocol for the therapeutic trial was completed in April 1978. 102 patients were randomized in the porphylactic trial and 51 in the therapeutic trial. The Recruitment and Intervention Phase ended in February 1980. The trial is now in the Analysis and Dissemination Phase.

Trial Results (Prophylactic Transfusion Study)

54 patients were randomized to receive daily granulocyte transfusions and 48 were randomized to the control group. Granulocyte transfusions were given for 28 days. The primary end-point was the occurrence of documented infection during the study period. Patients were monitored and data collected daily. Additional evaluations were performed 35 and 60 days after randomization and at six month intervals thereafter. The incidence of bacterial septicemia was significantly lower in patients given transfusions (9 per cent) than in controls (27 percent). The incidence of pneumonia was twice that in transfused patients than in controls. Granulocyte transfusion did not reduce the incidence of other infections or improve bone-marrow recovery, remission rate and duration, or survival. Seventy-two percent of the patients given transfusions had transfusion reactions and fifty-seven percent had pulmonary infiltrates versus twenty-seven percent of the controls. Thirty-five percent of the patients with pulmonary infiltrates died versus five percent of those without infiltrates. It was concluded that prophylactic granulocyte transfusions should not be used during remission-induction chemotherapy in acute myelogenous leukemia because the risks outweigh the benefits.

COOPERATIVE STUDY OF FACTOR VIII INHIBITORS

Objective

To test the efficacy of prothrombin complex concentrates (Factor IX) in the treatment of hemophiliac patients who have inhibitors to Factor VIII.

Summary Data

Mechanism: Contract (Institute Initiated Clinical Trial)
Initiation: July 1978
Total Duration: 2 years (Intervention: 1 year)
Funding:

Total Support Prior to FY 1981	$782,350
FY 1981 Support	0
Support Projected Beyond FY 1981	0
Total Support	$782,350

Subjects

Males, not stratified as to ethnic group, who had hemophilia.

Experimental Design

Double-blind study; patients served as their own controls. A total of 51 patients. Each patient received a single large dose of Konyne, Proplex, or diluted albumin (as a control). Joint bleeding of the elbow, knee, and ankle were evaluated 6 hours after each dose.

Current Phase (As of October 1981): Concluded

Background

Despite major advances in the treatment of patients with hemophilia, a serious remaining challenge is presented by the occurrence of circulating inhibitors to Factor VIII. Because of lack of information on the natural course of patients with Factor VIII inhibitors, the relative efficacy of various modes of therapy is not established. The Division of Blood Diseases and Resources decided to sponsor a clinical investigation which would evaluate populations of hemophilia patients for Factor VIII inhibitors, follow up these patients to provide information on the natural history of the inhibitor in the hemophilia patients, and make available a reference center to monitor results and attain uniformity.

Cooperative Study of
Factor VIII Inhibitors

Treatment of a patient with a severe inhibitor and consequent bleeding remains a problem. Management includes protracted treatment with Factor VIII, use of immunosuppressive agents, and most recently, the use of prothrombin complex (or Factor IX) concentrates. The rationale for Factor IX is that it bypasses the defect in Factor VIII caused by the inhibitor. This method of therapy has attracted wide popularity, but the success is greatly debated. It was intended at the very outset of the Factor VIII study that therapeutic trials involving patients with inhibitors would not be a prime function, but that such studies would be monitored if necessary. A control trial of Factor IX concentrates therapy was strongly advised by the DBDR Advisory Committee. Accordingly, during fiscal year 1978, a protocol for a double-blind control study was developed by the Factor VIII inhibitor group. The trial began in the spring of 1978, and the intervention concluded about 1 year later. The trial has been concluded.

Trial Results

Results were published in August 1980 indicating that although Factor IX, when used in a single dose, is only partially effective in the treatment of joint hemorrhage in hemophiliacs with inhibitors, its continued use for acute hemarthrosis is justified in the absence of any other effective and readily available therapy for this disorder.*

*Lusher, JM, Shapiro, SS, Palascak, JE, et al.: Efficacy of Prothrombin-Complex Concentrates in Hemophiliacs with Antibodies To Factor VIII. N Engl J. Med. 1980; 303:421-425.

MANAGEMENT OF PATENT DUCTUS IN PREMATURE INFANTS

Objective

To evaluate the effects (up to one year of age) of indomethacin on the clinical course of patent ductus arteriosus in premature infants (24 hours old or less) and to assess the relative merits of indomethacin and surgery in infants with persistent respiratory distress who were not treated early with indomethacin. Two concurrent trials are to be performed.

Summary Data

Mechanism: Grant (Investigator Initiated Clinical Trial)
Initiation: September 1978
Total Duration: 4 years (Intervention and Follow-up: 2 years)
Funding:

Total Support Prior to FY 1981	$3,543,332
FY 1981 Support	576,763
Support Projected Beyond FY 1981	0
Total Support	$4,120,095

Subjects

Premature infants with patent ductus arteriosus, males and females, with birth weights of 1,750 gm of less, admitted to the participating institutions within the first 24 hours of life. Total sample size was 400 for Trial A and 140 for Trial B.

Experimental Design

Trial A was a randomized, double-blind trial in which indomethacin plus usual medical therapy was compared with a placebo plus medical therapy. Where this regimen was unsuccessful, the code was broken, and infants who received indomethacin were treated surgically. Infants who had received placebo in Trial A were entered, if there are no contraindications to indomethacin, into Trial B. In Trial B, infants were randomized to immediate surgery or indomethacin therapy. Those in whom indomethacin treatment is unsuccessful were be treated surgically.

Current Phase (As of October 1981): Intervention (Follow-up)

Background

The incidence of patent ductus arteriosus is higher in premature infants than in full-term infants and is highest in premature infants who have respiratory distress syndrome. It is generally agreed that intervention in an asymptomatic infant with a small left-to-right shunt is unnecessary, since the patent ductus almost invariably closes spontaneously and thus does not require surgery. A few infants will demonstrate signs of a large shunt during the course of respiratory

distress syndrome. Many of these infants will improve with medical management of congestive heart failure, but others require surgical closure. A third group of babies with respiratory distress have severe progressive pulmonary disease requiring ventilatory support. There is disagreement as to whether elimination of the patent ductus in these infants results in decreased mortality. A variety of therapeutic approaches is being used, and there is no convincing evidence of the superiority of one treatment over another.

The Recruitment and Intervention Phase began in April 1979. Recruitment was completed March 31, 1981 with the recruitment goal of 400 patients met.

Preliminary Trial Results

At the time of hospital discharge, mortality and morbidity was very similar in the early indomethacin group, the delayed indomethacin group, and the usual medical therapy plus surgery group. However, in the two groups who received indomethacin, surgery was necessary to close the ductus in only 30% of cases, as opposed to 70% in the group who did not receive indomethacin. Thus, it appears that the use of indomethacin eliminates the need for surgery in 40% of the infants with this condition. All patients will be followed for one year after hospital discharge, with these results to be released in 1982.

HEPATITIS B VACCINE CLINICAL TRIAL

Objective

To determine the efficacy of a new vaccine to prevent hepatitis B.

Summary Data

Mechanism: Grant (Investigator Initiated Clinical Trial)
Initiation: November 1978
Total Duration: 3 years (2 years Intervention and Follow-up)
Funding:

Total Support Prior to FY 1981	$100,000	estimated
FY 1981 Support	100,000	"
Support Projected Beyond 1981	0	
	$200,000	"

Subjects

Males at high risk for hepatitis B virus infection, 36 years of age or younger, no recent symptoms of hepatitis, blood specimen negative for HB_sAg, anti-HB_s and anti-HB_e.

Experimental Design

Randomized, double blind, fixed-sample. Total sample size was 1083. 549 subjects were allocated to the vaccine group in which they were treated with highly purified formalin-inactivated virus subunits derived from the plasma of chronic carriers of hepatitis B. 534 were allocated to the placebo group. Both groups received injections at 0, 1 month, and 6 months unless evidence of infection developed before the series was completed.

Current Phase (As of October 1981): Concluded

Background

Although most carriers of HB_sAg are asymptomatic, a substantial proportion eventually develop chronic active hepatitis and cirrhosis. There is also overwhelming evidence that the hepatitis B virus is the single most important causative factor of hepatocellular carcinoma. Thus, mass immunization programs against HBV infection may ultimately affect not only the incidence of acute hepatitis B and the pool of chronic carriers but may also reduce the morbidity and mortality from chronic active hepatitis, cirrhosis, and hepatocellular carcinoma.

Krugman and his co-workers laid the groundwork for active immunization against hepatitis B in 1970 to 1973. They discovered that a 1:10 dilution of hepatitis B infective serum lost its infectivity when boiled for one minute but retained its antigenicity and prevented hepatitis B in 70% of vaccinated subjects. Hilleman and his colleagues at the Merck Institute of Therapeutic Research developed a more sophisticated vaccine consisting of highly

purified, formalin-inactivated HB_sAg particles derived from the plasma of chronic carriers of the antigen. By 1978, data were sufficient to permit testing in a clinical trial.

The first subject was inoculated in November 1978, and by October 1979, recruitment had ended. In May 1980, all trial events were reviewed and classified by an expert panel. In June 1980 the code of vaccine and placebo allocation was broken.

Trial Results

Within one month of the first vaccination, 31.4 percent of persons receiving the vaccine developed antibody against hepatitis B; within two months, this rate increased to 77 percent; within three months, to 87 percent; and within six months, but before the third injection, to 90 percent. The booster injection increased the antibody-response rate to 96 percent. Antibody-response rates then remained essentially unchanged for the rest of the 18-month followup period. The incidence of chemical or serologic evidence of hepatitis B in vaccine recipients varied between 1.4 percent and 7.6 percent compared with 18.1 percent and 35.0 percent in placebo recipients.

III: Recently Initiated Trials (FY 1981)

A RANDOMIZED TRIAL OF ASPIRIN AND MORTALITY IN PHYSICIANS

Objective

To assess the effect on cardiovascular mortality of alternate-day consumption of 325 milligrams of aspirin and, secondarily, the effect on cancer incidence of alternate-day consumption of 30 milligrams of beta-carotene.

Summary Data

Mechanism: Grant (Investigator Initiated Clinical Trial)
Initiation: September 1981
Total Duration: 5 years (Intervention 4.5 years)
Funding:

Total Support Prior to FY 1981	$ 0
FY 1981 Support	506,002*
Support Projected Beyond FY 1981	1,866,153
Total Support	$2,372,155

Subjects

Male physicians, age 50 to 75, who report no history of stroke, myocardial infarction, cancer, or renal disease, who indicate no contraindications to aspirin or beta-carotene and who report no current usage of aspirin or Vitamin A tablets greater than once per week. Sample size is estimated to be 21,900.

Experimental Design

Randomized, double-blind, fixed sample. Participants are to be randomized into one of four treatment groups: one 325 millligram aspirin tablet ever other day, alternating with one 30 milligram capsule of beta-carotene; one aspirin every other day, alternating with one capsule of beta-carotene; and one aspirin placebo tablet every other day, alternating with one capsule of beta-carotene placebo. Major endpoints for the cardiovascular component of the study are cardiovascular mortality, total mortality, and coronary events.

Current Phase (As of October 1981): Planning

Thrombosis plays a major role in the late stages of coronary occlusion. Platelet aggregation is a large component in the formation of arterial thrombi. In pharmacologic studies, aspirin has been shown to inhibit platelet aggregability and, therefore, might be expected to prevent coronary occlusion. These effects are apparent in the dose range of 100-1000 mg/day, and may be most evident at 160 milligrams daily. Higher doses seem to be no more effective in either inhibition of platelet aggregability or prolonged bleeding time.

*Joint funding by NHLBI and NCI. Total dollars spent in FY 1981 were $843,336. NHLBI financed $506,002 and NCI $337,334. Total dollars, including estimated indirect costs, committed through FY 1985 are $3,110,254, of which NHLBI is to fund $1,866,153 and NCI to fund $1,224,101.

PRIMARY PREVENTION OF HYPERTENSION (FEASIBILITY STUDY)

Objective

To determine whether hypertension can be prevented by dietary interventions in a population of 18-40 year old high risk men and women.

Summary Data

Mechanism: Grant (Investigator Initiated Clinical Trial)
Initiation: September 1981
Total Duration: 5 years (Feasibility Study)
Funding:

Total Support Prior to FY 1981	$ 0
FY 1981 Support	1,121,387
Support project Beyond FY 1981	9,811,873
Total Support	$10,933,260

Subjects

Males and females, ages 18-40, first degree relatives of hypertensive patients in the HDFP study, first degree relatives of clinic hypertension patients, and patients identified through screening. Patients will have initial home diastolic blood pressure between 78-96 mm Hg, subsequent clinic readings between 80-89 mm HG and Quetelet body mass index of more than 0.035 and less than 0.061. 800 patients will be required.

Experimental Design

Randomized, non-blind, with five groups of 160 patients each. The groups include: a control group with no intervention; a low sodium group with a goal of 70 milliequivalents sodium intake per day; a low sodium, high potassium group with a goal of 70 milliequivalents sodium and 100 milliequivalents potassium per day; a weight reduction group with a goal of more than five percent reduction in body weight; and a body weight reduction and low sodium intake group.

Current Phase (As of October 1981): Planning

Background

Animal studies conducted over recent decades have shown that excess dietary sodium chloride induces hypertension in a large fraction of most mammalian species and that excess dietary potassium chloride protects against the hypertensigenic action of excess sodium chloride. Human population groups which consume less than three grams of sodium chloride per day do not show the rise in blood pressure with increasing age that occurs in populations in industrial nations. A variety of studies have shown the relationship of body mass to blood pressure, leading many investigators to believe excess weight to be the leading risk factor for high blood pressure. Intervention trials have demonstrated that weight reduction in the absence of substantial change in sodium excretion results in reducing blood pressue in hypertensives. The study is in the Planning Phase, in which the protocol will be refined and the manual of operations developed. Included in the study are four clinical centers, a coordinating center, and a nutrition and education resource center.

IV. Trials in the Planning Stage

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ANTIARRHYTHMIC AGENTS IN THE PREVENTION OF SUDDEN DEATH: PILOT STUDY

Objective

To conduct a pilot study in order to compare the effectiveness of various drugs and drug combinations in suppressing ventricular arrhythmias, and to evaluate their safety. This pilot study will also assess the feasibility of carrying out a full scale clinical trial. The objective of the full trial, if it is conducted, will be to determine if the suppression of ventricular arrhythmias in people with coronary heart disease will result in reduction in sudden cardiac death.

Proposed:

Mechanism: Contract (Institute Initiated Clinical Trial)
Initiation: September 1982
Total Duration: 4 years (Pilot Study)
Funding:
Total Support $8,000,000

Subjects

Patients in the post-MI period who have major ventricular arrhythmias.

Experimental Design

About 500 patients would be enrolled and randomized to five groups. About 100 patients per group is required in order to obtain reliable information on toxicity and to analyze results by subgroups.

The drugs studied will be chosen from among amiodarone, aprindine, disopyramide, encainide, flecainide, lorcainide, mexiletine, procainamide, quinidine, and tocainide. Each group will follow a pre-determined treatment strategy. Initially, patients will be prescribed one of five drugs. After a three month interval, efficacy in decreasing ventricular arrhythmias will be assessed. Then, depending on the degree of arrhythmia suppression and occurrence of side effects, a second drug will supplement or replace the first drug.

Background

Approximately 400,000 people in the U.S. die suddenly every year, most of them presumably from cardiac arrhythmias. Three quarters of this population has known heart disease. Epidemiologic studies have indicated that complex ventricular premature beats make an independent contribution to risk of sudden death in survivors of myocardial infarction and do not appear to be merely a reflection of their association with

relatively severe myocardial damage. The potential for reduction in mortality by identification and administration of drugs capable of safely suppressing ventricular arrhythmias is tremendous. Currently, there is incomplete knowledge regarding which types of ventricular arrhythmias respond to various kinds of drugs. This pilot study of antiarrhythmic agents would help clarify this issue.

ISOLATED SYSTOLIC HYPERTENSION IN THE ELDERLY

Objective

To determine the effect of treating isolated systolic hypertension (ISH) in persons over 60 years of age.

Proposed

Mechanism: Contract (Institute Initiated Clinical Trial
Total Duration: 7 years (Intervention 3 years)
Funding:
Total support $70,000,000

Subjects

Males and females, over 60 years of age and with systolic blood pressure greater or equal to 160 mm Hg and a diastolic blood pressure less than 90 mm Hg. Total sample size is 4,000.

Experimental Design

Randomized, double blind, placebo controlled. All patients would be treated and followed for three years, the primary endpoint being the occurrence of stroke, or other cardiovascular events.

Background

The classical form of essential hypertension is a relative increase in both the systolic and the diastolic components of the blood pressure. Attention so far has primarily focused on elevated diastolic pressure and it has been shown, beyond doubt, that effective treatment of this condition results in not only reduced mortality, but also in a lesser risk of subsequent cardiovascular and renal complications. The prevalence of combined systolic-diastolic hypertension tends to stabilize in late middle age. However, with increasing years the systolic pressure continues to rise out of proportion to any concomitant rise in the diastolic component. Hence the emergence in the elderly population of the condition known as isolated systolic hypertension (ISH).

It was once believed that the complication of hypertension could be completely accounted for by the diastolic elevation alone. There is now abundant evidence that the systolic component is at least as equally predictive of future morbidity and mortality. Therefore effective treatment of ISH in the elderly population might reduce premature mortality and the occurrence of disabling cerebrovascular, cardiovascular and renal disease. ISH may also play an important part in the etiology of senile dementia.

To determine whether a large study is now feasible the National Heart, Lung, and Blood Institute is sponsoring, in conjunction with the National Institute on Aging, a pilot study of systolic hypertension in the elderly. This will recruit a total of 500 patients from five centers and treat and follow them all for at least one year. This small pilot has specific objectives each designed to test and evaluate critical components of a future full-scale endeavor directed at the consequences of treating ISH in the elderly.

STREPTOKINASE IN THE TREATMENT OF MYOCARDIAL INFARCTION

The use of intracoronary or intravenous streptokinase in the treatment of acute myocardial infarction is showing dramatic effects upon relieving acute coronary obstruction. This trial will assess the effectiveness of streptokinase under controlled clinical procedures in order to prevent inappropriate widespread clinical use without inadequate validation of net benefit. Details of this trial are under development.

EVALUATION OF VENTILATION-PERFUSION SCANS AND PULMONARY ANGIOGRAPHY FOR DIAGNOSIS OF PULMONARY EMBOLISM

Objective

To evaluate the effectiveness of ventilation-perfusion scans as a less dangerous and less costly alternative and adjunct technique to pulmonary angiography, for the diagnosis of pulmonary embolism. The outcome is expected to solve a major medical controversy with important implications for reducing the risks associated with the diagnosis and treatment of pulmonary embolism.

Proposed

Mechanism: Contract (Institute Initiated Clinical Trial)
Total Duration: 4 years (Recruitment 2 years)
Funding:
Total Support $70,000,000

Subjects

Patients suspected of having pulmonary embolism. Total sample size is 700.

Experimental Design

Non-randomized, non-blind, fixed sample. The trial would involve 700 patients who would receive ventilation perfusion scans; negative scans would result in detailed followup; equivocal and positive scans would lead to pulmonary angiography for definitive diagnosis and followup.

Background

Pulmonary embolism refers to a blood clot blocking one or more arteries in the lung. The problem is associated with patients recovering from major surgery, patients with poor circulation, childbirth, women taking oral contraceptives, and patients with underlying cancer. In the last decade despite diagnostic advances the condition remains difficult to diagnose. Postmortem exams have shown a high incidence of undiagnosed pulmonary emboli, conditions that in many cases may have been associated with the patient's death. Recent estimates indicate that pulmonary embolism may account for 50,000 deaths each year. If less than one embolic event in 10 is fatal, there are an estimated half a million episodes of pulmonary embolism each year in hospitalized patients in the United States.

The primary immediate hospital treatment for pulmonary embolism, anticoagulation therapy with heparin is dangerous, being the leading cause of adverse drug reactions in hospitalized patients. Moreover, the followup treatment with the oral anticoagulant coumadin represents some risk since that drug is one of the eight drugs most commonly responsible for hospital admission.

This trial will assess the accuracy of ventilation-perfusion scans, a radionucleide imaging technique, in diagnosing pulmonary embolism, comparing this technique to the more invasive and more dangerous, standard technique of pulmonary angiography.

SLOW CHANNEL CALCIUM BLOCKER IN PATIENTS WITH CORONARY ARTERY SPASM

Objective

To evaluate the efficacy of a slow channel calcium blocker in patients with coronary artery spasm.

Proposed

Mechanism: Contract (Institute Initiated Clinical Trial)
Total Duration: 6 years (Recruitment 2 years)
Funding:
Total Support $8,000,000

Subjects

Patients with coronary artery spasm. These patients would be identified primarily on the basis of angina at rest. However, a number of patients with chronic stable angina and acute myocardial infarction may also be shown to have coronary artery spasm and would be eligible for the study. The primary endpoint would be death plus nonfatal myocardial infarction. Reduction in angina would also be measured. Total sample size is 650.

Experimental Design

Double blind, multicenter, controlled trial.

Background

In recent years, there has been a resurgence of the concept that coronary artery spasm plays a major role in cardiac disease. The major area is thought to be unstable angina. However, there is some evidence that some people with chronic stable angina also have coronary artery spasm. In addition, studies have shown that of those with acute myocardial infarction, perhaps 5% have no evidence of vessel disease and 25% have evidence of only one vessel disease. Coronary artery spasm may play a role there as well.

Slow channel blockers (calcium antagonists) have received recent attention in the relief of the symptoms of cornary artery spasm. A number of small or uncontrolled studies have been done in patients with spasm and have shown promising results in relief of variant angina and ventricular arrhythmias (which often accompany variant angina). However, a large controlled study is needed to demonstrate whether these agents are indeed beneficial in reducing mortality and morbidity.

Previous studies have demonstrated the feasibility of identifying eligible patients and extended treatment with acceptable compliance and toxicity levels. A trial with about 10 centers is necessary to recruit the 650 patients necessary for a two-arm study. Recruitment would take two years, with one additional year of follow-up.

PHYSICAL EXERCISE IN SURVIVORS OF MYOCARDIAL INFARCTION

Objective:

To test the effect of physical exercise in survivors of myocardial infarction.

Proposed

Mechanism: Contract (Institute Initiated Clinical Trial)
Total Duration: 7 years (Recruitment 2 years)
Funding:
Total Support $50,000,000

Subjects

Post-myocardial infarction patients.

Experimental Design

Randomized, controlled trial. Four thousand subjects would be allocated either to Special Intervention, comprising an individually designed training program and risk factor counseling, or to Usual Care from their primary physicians.

Background

One third of all deaths in the United States are the direct result of coronary heart disease (CHD), making it the leading cause of death. The patient who survives an MI has not only an increased chance of dying but also risks significant morbidity from cardiovascular and renal complications. Myocardial infarction often comes at a time when a subject has significant responsibilities both at home and at work.

Of the approximately one million persons suffering their first coronary event each year, roughly 400,000 of them die in the acute phase. The 600,000 who survive face a 10% chance of dying in the first year after the event, resulting in an additional 60,000 deaths. Therefore a reduction of even twenty percent would result in a substantial saving of lives. In five exercise trials to date, while none demonstrated a significant reduction in mortality (perhaps because of inadequate sample size), all had a positive trend favoring the exercise group ranging from 18.8% to 37.0%. Any new trial undertaken in this area would need to be sufficiently large to permit a true beneficial effect on mortality to detected. To date, exercise appears to be one of the most promising interventions in a post-MI population. Increasing interest in this field by practicing physicians and the general population would most likely encourage participation in a post-MI clinical trial of physical exercise.

PREVENTION OF SUDDEN DEATH IN SURVIVORS OF OUT-OF-HOSPITAL VENTRICULAR FIBRILLATION

Objective

To evaluate an antiarrhythmic agent in patients who recover from out-of-hospital ventricular fibrillation.

Proposed

Mechanism: Contract (Institute Initiated Clinical Trial)
Total Duration: 5 years (Recruitment 2 years)
Funding:
Total Support $5,000,000

Subjects

Patients who have recovered from out-of-hospital ventricular fibrillation. Total size is 400.

Experimental Design

Randomized, multicenter trial.

Background

The number of community programs aimed at reducing heart disease mortality in the pre-hospital phase is increasing. The greater sophistication of ambulance and other rescue services plus the spread of cardiopulmonary resuscitation programs are likely to result in many more survivors of ventricular fibrillation. Recurrence of fibrillation is extremely likely in this population, especially in those without a demonstrable myocardial infarction accompanying the fibrillatory episode. In fact, there is often an absence of any other identifiable cardiac pathology. Therefore, if the ventricular fibrillation could be prevented, a major increase in life span might be expected. Currently, there is no accepted therapy which will prevent recurrence of fibrillation. At the same time, there are a number of promising, new antiarrhythmic drugs. Therefore, the time is appropriate to assess one or more of these drugs.

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